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877-708
TT/051

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,396,598

Issued: August 2, 1983

To: Youlin Lin

For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT

SOLICITOR

FEB 0 9 1989

U.S. PATENT & TRADEMARK OFFICE

TRANSMITTAL OF
APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 with regard to U.S. Pat. No. 4,396,598.

A check for the required fee of $550.00 is attached. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 02-2135. A duplicate of this sheet is enclosed for that purpose.

Respectfully submitted,

BERNARD, ROTHWELL & BROWN, p.c.

By George R. Repper
George R. Repper
Attorney for Applicant
Registration No. 31,414

1700 K Street, N.W.
Washington, D.C. 20006
Telephone: (202)833-5740

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,396,598

Issued: August 2, 1983

To: Youlin Lin

For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

Your Applicant, Mallinckrodt, Inc., a corporation under the laws of the state of Delaware, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,396,598 granted to Youlin Lin on the second day of August 1983 for a TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT, by virtue of the assignments recorded January 11, 1982, (Reel 3981, Frame 749) and February 14, 1986 (Reel 4572,Frames 403-418), copies attached hereto as Composite Exhibit A. Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 in accordance with 37 C.F.R. §1.740.

(1) The claims of U.S. Pat. No. 4,396,598 (copy attached as Exhibit B) are directed to a compound generically known as ioversol, designated chemically as N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide.

(2) Ioversol was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved products are OPTIRAY-160™ (ioversol injection 34%), OPTIRAY-240™ (ioversol injection 51%) and OPTIRAY-320™ (ioversol injection 68%). The approved products received permission for commercial marketing or use under

section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) when the new drug application thereon (NDA 19-710) was approved on December 30, 1988.

(4) The only active ingredient in the approved OPTIRAY™ products is ioversol. Ioversol had not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 19-710 by the Food and Drug Administration.

(5) This application for extension of patent term is being submitted within the 60 day period permitted under 37 C.F.R. §1.720(f), said period expiring on February 28, 1989.

(6) The complete identification of the patent for which extension of term is being sought is:

Inventor: Youlin Lin

Patent Number: United States Patent No. 4,396,598

Issue Date: August 2, 1983

Expiration Date: August 2, 2000

(7) Exhibit B is a complete copy of the patent identified in paragraph (6).

(8) No disclaimer, certificate of correction, or reexamination certificate has been issued with regard to U.S. Patent 4,396,598. Composite Exhibit C is a complete copy of a maintenance fee statement indicating receipt of the maintenance fee payment by the United States Patent and Trademark Office with regard to U.S. Patent 4,396,598.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(9)

(9) U.S. Patent 4,396,598 claims the approved product.

Specifically, claim 1 claims the active ingredient ioversol, as follows:

> CLAIM 1. N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide.

The approved product contains ioversol which is a generic name for the chemical claimed in claim 1.

Claim 2 claims a radiological composition containing the active ingredient ioversol, as follows:

> CLAIM 2. A radiological composistion containing N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

The approved product is a radiological composistion containing N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

Claim 3 claims a method for X-ray visualization using a radiological composition containing the active ingredient ioversol, as follows:

> CLAIM 3. In a method for X-ray visualization wherein a radiological composition containing an X-ray contrast vehicle is injected in a sufficient amount to provide adequate visualization and thereafter X-ray visualization carried out, the improvement comprising or utilizing as the radiological composition a composition containing N,N'-Bis(2,3-

dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

The approved product is used in a method for X-ray visualization wherein a radiological composition containing an X-ray contrast vehicle is injected in a sufficient amount to provide adequate visualization and thereafter X-ray visualization carried out, the improvement comprising or utilizing as the radiological composition a composition containing N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(10)

(10) The relevant dates and information, pursuant to 35 U.S.C. §156(g), to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) As shown in Composite Exhibit D, the Investigational New Drug Application (IND 27,630) for ioversol was filed on December 20, 1985 and became effective on January 22, 1986. (Note that the code name "MP-328" is used in many of the attached documents in place of the USANC approved name of ioversol. MP-328 and ioversol refer to the same product, which is the subject matter of the above-identified patent. The name "iovisatrol" was originally proposed to the USANC as a name for MP-328, but such proposal was not approved and the name "ioversol" was adopted instead.)

(ii) New Drug Application (NDA 19-710) for OPTIRAY™ (ioversol injection) was submitted on June 25, 1987 (Exhibit E); and

(iii) New Drug Application (NDA 19-710) for OPTIRAY™ (ioversol injection) was approved on December 30, 1988 (Exhibit F).

STATEMENT PURSUANT TO 37 CFR 1.740(a)(11)

(11) As a brief description of the activities undertaken by Applicant Mallinckrodt, Inc., during the applicable regulatory review period, a chronology of events leading up to approval of the subject product and of the major communications between the Applicant and the Food and Drug Administration concerning the product is being submitted herewith.

Exhibit G is a chronology of activities between August 8, 1985 and January 5, 1989, concerning IND 27,630.

Exhibit H is a chronology of activities between December 17, 1986 and January 11, 1989, concerning NDA 19-710.

Exhibit I is a Declaration of Niles B. Ross, declaring that Exhibits G and H accurately and correctly describe the activities set forth therein.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(12)

(12) Applicant is of the opinion that U.S. Patent 4,396,598 is eligible for extension of patent term under 35 U.S.C. §156 because said patent satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. 156(a)

U.S. Patent 4,396,598 claims a product.

(b) 35 U.S.C. §156(a)(1)

The term of U.S. Patent 4,396,598 has not expired before the submission of this application.

(c) 35 U.S.C. §156(a)(2)

The term of U.S. Patent 4,396,598 has never been extended.

(d) 35 U.S.C. §156(a)(3)

The application for extension of patent term is submitted by the authorized agent of the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and with the rules of the United States Patent and Trademark Office.

(e) 35 U.S.C. §156(a)(4)

The product OPTIRAY™ has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. 156(a)(5)(A)

The commercial marketing or use of the product, OPTIRAY™, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) under which said regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4)

No other patent has been extended for the same regulatory review period for the product OPTIRAY™.

LENGTH OF EXTENSION CLAIMED

(h) The length of extension of the patent term of U.S. Patent 4,396,598 claimed by Applicant is 813 days or 2.22 years (see worksheet attached as Exhibit J). The length of extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(1) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began on January 22, 1986 and ended on December 30, 1988 which is a total of 1,073 days or 2.93 years which is the sum of (A) and (B) immediately below:

(A) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the "Testing Period", began on January 22, 1986 and ended on June 25, 1987, which is 519 days or 1.42 years, and

(B) The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period", began on June 25, 1987 and ended on December 30, 1988 which is 554 days or 1.51 years.

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (12)(h)(1) above (1,073 days) less the sum of:

(A) The number of days in the regulatory period which were on or before the date on which the patent issued (August 2, 1983) which is zero (0) days, and

(B) The number of days during the regulatory review period during which Applicant did not act with due diligence, which is zero (0) days, and

(C) One-half the number of days determined in sub-paragraph (12)(h)(1)(A) after the patent issued which is 260 days,

which is 813 days (1,073 days less 260 days);

(3) The number of days as determined in sub-paragraph (12)(h)(2), i.e., 813 days, when added to the

original term of the patent would result in the date, October 24, 2002;

(4) Fourteen (14) years, when added to the date of NDA approval (December 30, 1988), would result in the date December 30, 2002;

(5) The earlier date as determined in sub-paragraphs (12)(h)(3) and (4) is October 24, 2002;

(6) Since the original patent was issued prior to September 24, 1984 and no request for an exemption under subsection (1) of the Section 5 of the Federal Food, Drug and Cosmetic Act was submitted before September 24, 1984, 5 years when added to the original expiration date of the patent (August 2, 2000) would result in the date August 2, 2005;

(7) The earlier date as determined is sub-paragraphs (12)(h)(5) and (6) is October 24, 2002.

Therefore the length of extension of patent term claimed by Applicant is 813 days or 2.22 years.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(13)

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension of term sought.

(14) A check for the prescribed fee of $550.00 is attached. Any deficiency is to be charged to Deposit Account 02-2135 as is authorized in the accompanying transmittal letter, which is submitted in duplicate.

(15) Direct all inquires and correspondence relating to this application to:

George R. Repper
Bernard, Rothwell and Brown
1700 K Street, NW
Washington, DC 20006
(202) 833-5740

(16) A certified duplicate of this application is being submitted herwith.

(17) The requisite declaration pursuant to 37 C.F.R. §1.740(b) is attached hereto as Exhibit K.

(18) An Associate Power of Attorney is attached hereto as Exhibit L.

Respectfully submitted,

BERNARD, ROTHWELL & BROWN, p.c.

By 
George R. Repper
Attorney for Applicant
Registration No. 31,414

1700 K Street, N.W.
Washington, D.C. 20006
Telephone: (202)833-5740

Return to:

R.J. Klostermann

Mallinckrodt, Inc.
2nd & Mallinckrodt Streets
St. Louis, Missouri 63147

P.O. Box 5840
63134

Serial No. _____

Filed _____

ASSIGNMENT

WHEREAS, I, Youlin Lin, of Chesterfield, Missouri have invented certain improvements in Chemical Compounds, identified as 0225, and described in a patent application executed by me on the date _____ set after my signature _____ hereto: and

WHEREAS, Mallinckrodt, Inc., of St. Louis, Missouri, a corporation of the State of Missouri, is desirous of acquiring the entire right, title and interest in and to said invention or inventions and any and all patents to be obtained therefor;

NOW, THEREFORE, in consideration of Five Dollars ($5.00), the receipt of which is hereby acknowledged, and other valuable consideration, I do hereby sell, assign and transfer unto said Mallinckrodt, Inc., its successors and assigns, the entire right, title and interest in and to said invention or inventions, as described in the aforesaid application, in any form or embodiment thereof, and in and to the aforesaid application; and in and to any applications filed in any foreign country based thereon, including the right to file said foreign applications under the provisions of the International Convention; also any improvements on said invention or inventions now or hereafter made by me during the period of my employment; also the entire right, title and interest in and to any and all patents or reissues or extensions thereof to be obtained in this or any foreign country upon said invention, inventions, or improvements and any divisional, continuation, continuation-in-part or substitute applications which may be filed upon said invention, inventions, or improvements in this or any foreign country; and I hereby authorize and request the issuing authority to issue any and all patents on said application or applications to said Mallinckrodt, Inc., as assignee of the entire interest.

I further agree, without any payment by Mallinckrodt, Inc. other than expenses incurred by the undersigned, to communicate to said Mallinckrodt, Inc., its representatives or agents, any facts relating to said invention, inventions or improvements, including evidence for interference purposes or for other legal proceedings, whenever requested; testify in any interference or other legal proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective.

IN TESTIMONY WHEREOF, I have hereunto set my hand _____ and seal _____ on the date _____

set after my signature _____.

(L. S.) Youlin Lin, January 6, 19 82

(L. S.) _____, _____, 19 _____

(L. S.) _____, _____, 19 _____

State of Missouri
County of St. Louis } es.

On this 6th day of January, 19 82, before me personally appeared

Youlin Lin

to me known to be the person described in and who executed the foregoing instrument, and acknowledged that he executed the same as his free act and deed. In testimony whereof I have hereunto set my hand and official seal the day and year last above written.

(seal) Louise Kelley
Notary Public.

My Commission expires April 23, 1982

RECORDED
PATENT & TRADEMARK OFFICE
JAN 19 1982

LOUISE KELLEY
NOTARY PUBLIC, STATE OF MISSOURI
MY COMMISSION EXPIRES 4/23/82
ST. LOUIS COUNTY

State of _____
_____ of _____ } ss.

COMMISSIONER OF PATENTS AND TRADEMARKS

On this _____ day of _____, 19 _____, before me personally appeared

_____

to me known to be the person described in and who executed the foregoing instrument, and acknowledged that _____ executed the same as _____ free act and deed. In testimony whereof I have hereunto set my hand and official seal the day and year last above written.

(seal) _____
Notary Public.

My Commission expires _____

NO. 640

REEL 398 | FRAME 749

EXHIBIT
A
4,396,598

Mallinckrodt, Inc.

675 McDONNELL BLVD. • P.O. BOX 5840 • ST. LOUIS, MO. 63134 • (314) 895-2000

February 7, 1986

The Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Re: Patents

Dear Sir:

Please record the enclosed assignment by Mallinckrodt, Inc. to Malco, Inc. and then record the amendment of the Certificate of Incorporation of Malco, Inc. to Mallinckrodt, Inc.

Please charge the cost of recording this two-step transaction to deposit account 13-1160.

Sincerely,

(Mrs.) Grace J. Fishel
Senior Patent and
Trademark Attorney

GJF/de

Enclosures

20289 02/20/86 [illegible] 13-1160 020 518 7.00CH

~~91241755~~

21236303

Mallinckrodt

CERTIFICATE OF AMENDMENT
OF
CERTIFICATE OF INCORPORATION
OF
MALCO, INC.

MALCO, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware ("Malco"), does hereby certify:

The amendment to Malco's Certificate of Incorporation set forth in the following resolution approved by Malco's Board of Directors and stockholders was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware:

RESOLVED, that the Certificate of Incorporation of Malco be amended by striking Article One in its entirety and replacing therefor:

"1. The name of the corporation is Mallinckrodt, Inc."

This amendment to Malco's Certificate of Incorporation shall be effective on the later to occur of filing by the Secretary of State or January 2, 1986 at 10:30 a.m., Eastern Standard Time.

IN WITNESS WHEREOF, MALCO, INC. has caused this Certificate to be signed and attested by its duly authorized officers, as of this first day of January, 1986.

MALCO, INC.

BY: John L. Ufheil
John L. Ufheil
Executive Vice President

ATTEST:

Jake A. Larimer
Jake A. Larimer
Assistant Secretary

6. THE UNITED STATES PATENTS ARE AS FOLLOWS:

Our File #	Pat. No.	Issue Date
1634.1	3,413,340	11/26/68
1671	3,446,837	5/27/69
1690	3,403,983	10/1/68
1696	3,413,349	11/26/68
1711.1	3,582,401	6/1/71
1718.1	3,423,027	1/21/69
1720	3,455,818	7/15/69
1720.1	3,549,486	12/22/70
1722.1	3,492,145	1/27/70
1725	3,446,965	5/27/69
1725.1	3,535,085	10/20/70
1741.2	3,598,751	8/10/71
1745	3,437,677	4/8/69
1746.1	3,575,876	4/20/71
1747	3,684,929	8/15/72
1748	3,506,832	4/14/70
1753	3,537,428	11/3/70
1759	3,576,756	4/27/71
1761.1	3,781,338	12/25/73
1762	3,508,709	4/28/70
1763	3,575,877	4/20/71
1766	3,595,808	7/27/71
1769	3,668,141	6/6/72
1776	3,655,981	4/11/72
1779.1	3,814,769	6/4/74
1782	3,710,118	1/9/73
1785	Des. 217,995	7/7/70
1789	3,531,644	9/29/70
1793.1	3,478,038	11/11/69
1831	3,655,985	4/11/72
1836	3,673,519	6/27/72
1837	3,678,067	7/18/72
1838	3,709,826	1/9/73
1839	3,714,344	1/30/73
1843.1	3,705,933	12/12/72
1848	3,661,792	5/9/72
1864	3,723,075	3/27/73
1869	3,436,354	4/1/69
1870	3,509,919	5/5/70
1875	3,745,211	7/10/73
1881	3,799,740	3/26/74
1883	Des. 230,324	2/5/74
1894	3,833,509	9/3/74
1922	3,863,004	1/28/75
1933	3,830,746	8/20/74
1941.1	3,925,020	12/9/75
1948	3,912,935	10/14/75
1956	3,882,315	5/6/75
1958	3,962,412	6/8/76

0080	3,777,761	12/11/73
0081	3,853,130	12/10/74
0082	Des. 236,920	9/23/75
0083	4,150,676	4/24/79
0085	4,109,659	8/29/78
0094	4,203,096	5/13/80
0098	4,214,593	7/29/80
0101	4,224,440	9/23/80
0103	4,160,015	7/3/79
0104	4,245,685	1/20/81
0106	4,230,845	10/28/80
0108	4,176,138	11/27/79
0115	4,219,349	8/26/80
0116	4,256,719	3/17/81
0117	4,284,620	8/18/81
0122	4,298,592	11/3/81
0123	4,273,867	6/16/81
0125	4,242,274	12/30/80
0127	4,342,315	8/3/82
0128	4,271,202	6/6/81
0129	4,296,785	10/27/81
0131	4,038,434	7/26/77
0132	4,162,155	7/24/79
0133	3,903,029	9/2/75
0134	4,224,247	9/23/80
0135	4,256,669	3/17/81
0137	3,383,416	5/14/68
0154	4,264,529	4/28/81
0158	4,299,770	11/10/81
0159	4,340,859	7/20/82
0160	4,321,368	3/23/82
0185	4,357,258	11/2/82
0186	4,309,564	1/5/82
0190	4,307,249	12/22/81
0192	4,369,794	1/25/83
0193	4,329,314	5/11/82
0194	4,362,166	12/7/82
0195	4,387,711	6/14/83
0199	4,438,209	3/20/84
0200	4,440,954	4/3/84
0203	4,418,229	11/29/83
0225	4,396,598	8/2/83
0234	4,415,753	11/15/83
0239	4,539,428	9/3/85
0243	4,469,787	9/4/84
0245	4,464,176	8/7/84
0246	Des. 268,871	5/3/83
0251	4,551,551	11/5/85
0255	4,501,920	2/26/85
0256	4,471,134	9/11/84
0260	4,429,829	2/7/84
0262	4,490,400	12/25/84
0272	4,556,566	12/3/85
0273	4,556,567	12/3/85
0274	4,556,568	12/3/85
0275	4,556,577	12/3/85
0276	4,560,574	12/24/85
0278	4,556,578	12/3/85
0281	3,403,207	9/24/68

1979	4,125,709	11/14/78
1982	3,966,896	6/29/76
5117.1	3,597,250	8/3/71
5131	3,560,380	2/2/71
5251	3,674,501	7/4/72
5266.1	3,647,492	3/7/72
5267.1	3,850,838	11/26/74
5289	3,656,982	4/18/72
5316.1	3,803,292	4/9/74
5316.1.1	3,882,251	5/6/75
5327	3,743,668	7/3/73
5375	3,909,472	9/30/75
5384	3,890,368	6/17/75
W-101	3,717,680	2/20/73
W-102	3,694,508	9/26/72
W-103	3,703,598	11/21/72
W-104 CA2	3,917,695	11/4/75
W-105	3,748,358	7/24/73
CH-0001	3,917,671	11/4/75
0002	3,953,497	4/27/76
0011	3,907,976	9/23/75
0013	4,075,334	2/21/78
0014	4,064,227	12/20/77
0015	4,062,933	12/13/77
0016	4,048,296	9/13/77
0017	3,991,173	11/9/76
0021	4,014,651	3/29/77
0023	4,082,747	4/4/78
0024	4,225,725	9/30/80
0032	4,003,903	1/18/77
0036	3,948,958	4/6/76
0037	4,089,873	5/16/78
0038	4,054,566	10/18/77
0042	4,069,250	1/17/78
0043	4,060,558	11/29/77
0044	4,075,314	2/21/78
0046	4,111,656	9/5/78
0050	4,066,743	1/3/78
0052	4,110,076	8/29/78
0058	4,018,831	4/19/77
0060	4,112,238	9/5/78
0062	4,314,055	2/2/82
0066	4,307,072	12/22/81
0067	4,159,993	7/3/79
0068	4,138,589	2/6/79
0072	3,589,368	6/29/71
0073	3,508,554	4/28/70
0074	3,595,241	7/27/71
0075	3,610,242	10/5/71
0076	3,612,050	10/12/71
0077	3,605,750	9/20/71
0078	3,613,684	10/19/71
0079	3,625,793	12/7/71

0282	3,766,267	10/16/73
0283	3,855,290	12/17/74
0284	4,012,398	3/15/77
0285	4,026,818	5/31/77
0286	4,038,294	7/26/77
0287	4,078,054	3/7/78
0288	4,333,920	6/8/82
0289	4,342,706	8/3/82
0291	4,457,911	7/3/84
0293	4,497,744	2/5/85
0296	4,504,462	3/12/85
0298	4,440,738	4/3/84
0299	4,504,463	3/14/85
0301	4,510,125	4/9/85
0308	3,422,137	1/14/69
0309	3,983,227	9/28/76
0310	4,229,427	10/21/80
0311	4,232,000	11/4/80
0312	4,233,284	11/11/80
0313	4,234,562	11/18/80
0315	4,496,576	1/29/85
0318	4,532,352	7/30/85
0326	4,554,849	11/26/85
0341	4,247,534	1/27/81
0405	4,515,774	5/7/85
0451	4,529,003	7/16/85
0453	4,116,387	9/26/78
0454	4,456,179	6/26/84
0458	4,251,033	2/17/81

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0182	156,661	6/5/80
0188	184,290	9/5/80
0189	198,019	10/17/80
0206	270,738	6/5/81
0207	250,219	4/2/81
0223	301,202	9/11/81
0224	332,335	12/18/81
0226	249,463	3/31/81
0232	344,334	2/1/82
0248	369,743	4/19/82
0252	412,468	8/30/82
0253	412,488	8/30/82
0263	495,843	1/17/83
0264	471,031	3/1/83
0265	467,939	2/18/83
0266	476,567	3/18/83
0267	467,565	3/18/83

0268	449,423	12/13/82
0271	502,067	6/7/83
0290	229,383	1/28/81
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0314	543,433	10/19/83
0319	546,051	10/27/83
0324	547,664	11/1/83
0337	570,199	1/12/84
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0407	626,781	7/2/84
0410	638,431	8/6/84
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0416	736,659	5/22/85
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0467	735,288	5/17/85
0468	754,133	7/12/85
0469	763,847	8/8/85
0470	767,548	8/20/85
0471	756,580	7/19/85
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0485	809,912	12/17/85
0486	809,940	12/17/85
0487	816,478	1/6/86
0488	816,479	1/6/86
0489	816,480	1/6/86
0490	816,481	1/6/86

8. IN WITNESS WHEREOF, MALLINCKRODT has caused these presents to be executed by its officer thereunto duly authorized and its corporate seal to be affixed as of the 2nd day of January, 1986, at St. Louis, Missouri, U.S.A.

MALLINCKRODT, INC.

By Raymond M. Gruber

Title Vice President

(Corporate Seal)

Attest:

Roger A. Keller

Assistant Secretary

ACKNOWLEDGMENT

STATE OF Missouri)
) SS.
COUNTY OF St. Louis)

On this 2nd day of January, 1986, before me personally came Raymond M. Gruber, to me known, who, being by me duly sworn, did depose and say that he is Vice President of MALLINCKRODT, INC., the corporation described in and which executed the above instrument; that he knows the seal of said corporation; that the seal affixed to said instrument is such

State of Delaware

Office of Secretary of State

I, MICHAEL HARKINS, SECRETARY OF STATE OF THE STATE OF DELAWARE DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF MALCO, INC. FILED IN THIS OFFICE ON THE SECOND DAY OF JANUARY, A.D. 1986, AT 4:16 O'CLOCK P.M.

RECORDED
PATENT & TRADEMARK OFFICE
FEB 7 1986

DEPARTMENT OF STATE
OFFICE OF THE SECRETARY OF STATE
1683 1793 1920
DELAWARE

726015041

Michael Harkins, Secretary of State

AUTHENTICATION: 0715436

DATE: 01/15/1986

ASSIGNMENT

1. WHEREAS, MALLINCKRODT, INC., a Missouri corporation, of St. Louis, Missouri (hereinafter referred to as MALLINCKRODT), is the owner of certain inventions and certain United States letters patent and U.S. pending applications, and

2. WHEREAS, MALCO, INC., a Delaware Corporation, of St. Louis, Missouri (hereinafter referred to as ASSIGNEE) is desirous of acquiring MALLINCKRODT's right, title and interest in and to said inventions and patents;

3. NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) and other good and valuable consideration by ASSIGNEE to MALLINCKRODT in hand paid, receipt of all of which is hereby acknowledged, MALLINCKRODT has agreed to and does hereby sell, assign, and transfer unto ASSIGNEE, its successors and assigns, all of MALLINCKRODT's right, title and interest in and throughout the United States in and to said inventions, said United States letters patent and any divisional, continuing, reissue or other patent applications based in whole or in part thereon, or based upon said inventions, and any letters patent which have been or may be granted thereon, including MALLINCKRODT's full right to sue for and recover all damages, if any, recoverable from past infringements of any of said letters patent; including specifically, without limiting the generality of the foregoing, the United States patents listed below.

4. TO BE HELD AND ENJOYED BY ASSIGNEE, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by MALLINCKRODT had this sale and assignment not been made.

5. MALLINCKRODT hereby authorizes and requests the United States Commissioner of Patents and Trademarks to issue any and all U.S. patents which may be granted upon said United States patent applications to ASSIGNEE, its successors and assigns.

6. THE UNITED STATES PATENTS ARE AS FOLLOWS:

Our File #	Pat. No.	Issue Date
1634.1	3,413,340	11/26/68
1671	3,446,837	5/27/69
1690	3,403,983	10/1/68
1696	3,413,349	11/26/68
1711.1	3,582,401	6/1/71
1718.1	3,423,027	1/21/69
1720	3,455,818	7/15/69
1720.1	3,549,486	12/22/70
1722.1	3,492,145	1/27/70
1725	3,446,965	5/27/69
1725.1	3,535,085	10/20/70
1741.2	3,598,751	8/10/71
1745	3,437,677	4/8/69
1746.1	3,575,876	4/20/71
1747	3,684,929	8/15/72
1748	3,506,832	4/14/70
1753	3,537,428	11/3/70
1759	3,576,756	4/27/71
1761.1	3,781,338	12/25/73
1762	3,508,709	4/28/70
1763	3,575,877	4/20/71
1766	3,595,808	7/27/71
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1776	3,655,981	4/11/72
1779.1	3,814,769	6/4/74
1782	3,710,118	1/9/73
1785	Des. 217,995	7/7/70
1789	3,531,644	9/29/70
1793.1	3,478,038	11/11/69
1831	3,655,985	4/11/72
1836	3,673,519	6/27/72
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1838	3,709,826	1/9/73
1839	3,714,344	1/30/73
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1870	3,509,919	5/5/70
1875	3,745,211	7/10/73
1881	3,799,740	3/26/74
1883	Des. 230,324	2/5/74
1894	3,833,509	9/3/74
1922	3,863,004	1/28/75
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1982	3,966,896	6/29/76
5117.1	3,597,250	8/3/71
5131	3,560,380	2/2/71
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5327	3,743,668	7/3/73
5375	3,909,472	9/30/75
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W-101	3,717,680	2/20/73
W-102	3,694,508	9/26/72
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0002	3,953,497	4/27/76
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0037	4,089,873	5/16/78
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0042	4,069,250	1/17/78
0043	4,060,558	11/29/77
0044	4,075,314	2/21/78
0046	4,111,656	9/5/78
0050	4,066,743	1/3/78
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0058	4,018,831	4/19/77
0060	4,112,238	9/5/78
0062	4,314,055	2/2/82
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0067	4,159,993	7/3/79
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0072	3,589,368	6/29/71
0073	3,508,554	4/28/70
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0075	3,610,242	10/5/71
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0081	3,853,130	12/10/74
0082	Des. 236,920	9/23/75
0083	4,150,676	4/24/79
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0094	4,203,096	5/13/80
0098	4,214,593	7/29/80
0101	4,224,440	9/23/80
0103	4,160,015	7/3/79
0104	4,245,685	1/20/81
0106	4,230,845	10/28/80
0108	4,176,138	11/27/79
0115	4,219,349	8/26/80
0116	4,256,719	3/17/81
0117	4,284,620	8/18/81
0122	4,298,592	11/3/81
0123	4,273,867	6/16/81
0125	4,242,274	12/30/80
0127	4,342,315	8/3/82
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0134	4,224,247	9/23/80
0135	4,256,669	3/17/81
0137	3,383,416	5/14/68
0154	4,264,529	4/28/81
0158	4,299,770	11/10/81
0159	4,340,859	7/20/82
0160	4,321,368	3/23/82
0185	4,357,258	11/2/82
0186	4,309,564	1/5/82
0190	4,307,249	12/22/81
0192	4,369,794	1/25/83
0193	4,329,314	5/11/82
0194	4,362,166	12/7/82
0195	4,387,711	6/14/83
0199	4,438,209	3/20/84
0200	4,440,954	4/3/84
0203	4,418,229	11/29/83
0225	4,396,598	8/2/83
0234	4,415,753	11/15/83
0239	4,539,428	9/3/85
0243	4,469,787	9/4/84
0245	4,464,176	8/7/84
0246	Des. 268,871	5/3/83
0251	4,551,551	11/5/85
0255	4,501,920	2/26/85
0256	4,471,134	9/11/84
0260	4,429,829	2/7/84
0262	4,490,400	12/25/84
0272	4,556,566	12/3/85
0273	4,556,567	12/3/85
0274	4,556,568	12/3/85
0275	4,556,577	12/3/85
0276	4,560,574	12/24/85
0278	4,556,578	12/3/85
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0283	3,855,290	12/17/74
0284	4,012,398	3/15/77
0285	4,026,818	5/31/77
0286	4,038,294	7/26/77
0287	4,078,054	3/7/78
0288	4,333,920	6/8/82
0289	4,342,706	8/3/82
0291	4,457,911	7/3/84
0293	4,497,744	2/5/85
0296	4,504,462	3/12/85
0298	4,440,738	4/3/84
0299	4,504,463	3/14/85
0301	4,510,125	4/9/85
0308	3,422,137	1/14/69
0309	3,983,227	9/28/76
0310	4,229,427	10/21/80
0311	4,232,000	11/4/80
0312	4,233,284	11/11/80
0313	4,234,562	11/18/80
0315	4,496,576	1/29/85
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0488	816,479	1/6/86
0489	816,480	1/6/86
0490	816,481	1/6/86

8. IN WITNESS WHEREOF, MALLINCKRODT has caused these presents to be executed by its officer thereunto duly authorized and its corporate seal to be affixed as of the 2nd day of January, 1986, at St. Louis, Missouri, U.S.A.

MALLINCKRODT, INC.

By Raymond M. Fisher

Title Vice President

(Corporate Seal)

Attest:

Roger A. Keller

Assistant Secretary

ACKNOWLEDGMENT

STATE OF Missouri)
) SS.
COUNTY OF St. Louis)

On this 2nd day of January, 1986, before me personally came Raymond M. Fisher, to me known, who, being by me duly sworn, did depose and say that he is Vice President of MALLINCKRODT, INC., the corporation described in and which executed the above instrument; that he knows the seal of said corporation; that the seal affixed to said instrument is such

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REEL 4572 FRAME 417

corporate seal; that it was so affixed by order of the Board of Directors of said corporation; and that he signed his name thereto by like order. My commission expires:

Grace J. Fiehel, Notary Public
St. Louis County, State of Missouri
My Commission Expires Dec. 18, 1937

Grace J. Fiehel
Notary Public

(Notarial Seal)

United States Patent [19]

Lin

[11] 4,396,598

[45] Aug. 2, 1983

[54] **TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT**

[75] Inventor: Youlin Lin, Chesterfield, Mo.

[73] Assignee: Mallinckrodt, Inc., St. Louis, Mo.

[21] Appl. No.: 338,382

[22] Filed: Jan. 11, 1982

[51] Int. Cl.³ A61K 49/04; C07C 103/24

[52] U.S. Cl. 424/5; 564/156

[58] Field of Search 424/5; 564/156

[56] **References Cited**

U.S. PATENT DOCUMENTS

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Primary Examiner—Bernard Helfin

Attorney, Agent, or Firm—R. J. Klostermann; L. N. Goodwin

[57] **ABSTRACT**

Novel X-ray contrast agents, i.e., N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide.

3 Claims, No Drawings

TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT

The present invention relates to new compounds, to radiological compositions containing such compounds and to the use of such radiological compositions.

Non-ionic contrast agents for intravascular and central nervous system visualization are complex molecules. As is known, the iodine in the molecule provides opacification to the X-rays. The remainder of the molecule provides the framework for transport of the iodine atoms. However, the structural arrangement of the molecule is important in providing stability, solubility and biological safety in various organs. A stable carbon-iodine bond is achieved in most compounds by attaching it to an aromatic nucleus. An enhanced degree of solubility as well as safety is conferred on the molecule by the addition of suitable solubilizing and detoxifying groups.

Several of the features that are desirable for intravascular and central nervous system non-ionic contrast agents are often incompatible so that all such agents represent compromises. In searching for the best compromise, the controlling factors are pharmacological inertness, i.e., in vivo safety, and high water solubility. Thus, the ideal intravascular or central nervous system non-ionic agent represents a compromise in an attempt to obtain the following criteria:

1. Maximum opacification to X-rays
2. Pharmacological inertness
3. High water solubility
4. Stability
5. Selective excretion
6. Low viscosity
7. Minimal osmotic effects

An object of the present invention is to provide a non-ionic X-ray contrast agent. Another object of this invention is to provide a non-ionic X-ray contrast agent meeting substantially all the foregoing criteria.

This invention relates to N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide. N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide is subject to a number of different types of isomerism as is explained below. The present invention extends to all isomers thereof. As used herein, the term N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide means N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide and all isomers thereof.

Exo and endo isomers exist due to restricted rotation of the N-CO bond caused by steric hindrance and the presence of the hydroxyethyl group. These isomers tend to equilibrate in solution but are sufficiently stable to be separated by thin layer chromatography.

In addition, there are two forms for each isomer due to restricted rotation of the N-(2-hydroxyethyl)-Ar bond. The compounds of the present invention also exist in racemic, optically active and meso forms.

Individual stereoisomers of the compounds of the invention can be obtained by conventional methods.

N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide may be used as an X-ray contrast agent. The agent may be used in various radiographic procedures including those involving cardiography, coronary arteriography, aortography, cerebral and peripheral angiography, arthrography, intraveneous pyelography and urography as well as myelography. Mixtures of isomers of this invention may also be used as X-ray contrast agents.

A further feature of the present invention is a radiological composition containing N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide as an X-ray contrast agent together with a pharmaceutically acceptable radiological vehicle.

Pharmaceutically acceptable radiological vehicles include those that are suitable for injection such as aqueous buffer solutions, e.g., tris(hydroxymethyl)aminomethane (and its salts), phosphate, citrate, bicarbonate, etc., sterile water for injection, physiological saline, and balanced ionic solutions containing chloride and/or bicarbonate salts of normal blood plasma cations such as Ca, Na, K and Mg. Other buffer solutions are described in *Remington's Practice of Pharmacy, Eleventh Edition* for example on page 170. The vehicles may contain a chelating agent, e.g. a small amount, of ethylenediaminetetraacetic acid, the calcium disodium salt or other pharmaceutically acceptable chelating agents.

The concentration of N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in the pharmaceutically acceptable vehicle, for example an aqueous medium, varies with the particular field of use. A sufficient amount is present to provide satisfactory X-ray visualization. For example, when using aqueous solutions for angiography the concentration of iodine is generally 140–400 mg/ml and the dose is 25–300 ml.

The radiological composition is administered so that the contrast agent remains in the living animal body for about 2 to 3 hours, although both shorter and longer residence periods are normally acceptable. N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide may thus be formulated for vascular visualization conveniently in vials or ampoules containing 10 to 500 ml. of an aqueous solution.

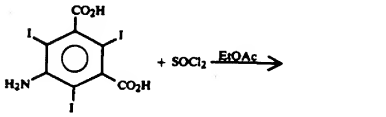
The radiological composition may be used in the usual way in X-ray procedures. For example, in the case of selective coronary arteriography, a sufficient amount of the radiological composition to provide adequate visualization, is injected into the coronary system and then the system is scanned with a suitable machine, for example a fluoroscope.

N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide may be prepared in accordance with the procedures set out below. All temperature designations are in degrees centigrade.

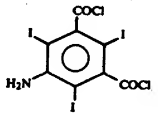
EXAMPLE I

Preparation of N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide (11)

A. Preparation of 5-Amino-2,4,6-triiodoisophthaloyl Chloride (2)



1

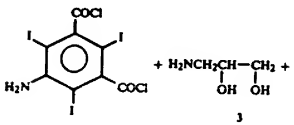


2

5-Amino-2,4,6-triiodoisophthalic acid (6.73 Kg, 12.04 mol) 1 was charged and EtOAc was added. $SOCl_2$ (5.73 Kg, 48.17 mol) was added to the slurry in one portion and the mixture was heated at reflux for 4 hours. After the reaction, 24.2 L of unreacted $SOCl_2$ and the solvent were distilled (64°-77°, 7 hrs. distillation time). The product started to precipitate when the reaction solution cooled to 55°; the slurry was stirred overnight, allowing it to cool to room temperature. The solids were collected, washed with cold EtOAc (5°, 3.8 L), suction-dried for 3 hours and air-dried at room temperature to give the desired product 2 (3.525 kg, 49.2% yield).

The filtrate (about 25 L) was distilled to a volume of 15 L and cooled to 2° overnight. The precipitated product was collected, washed with cold EtOAc (5°, 1.5 L), suction-dried and air-dried to give a second crop of the product 2 (0.83 kg, 11.6% yield). The two crops of the product were combined, 4.355 kg (60.8% yield). The product showed one spot by tlc analysis ($C_6H_5CH_3/CH_3OH$; 9/1).

B. Preparation of 5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (4)



2 3

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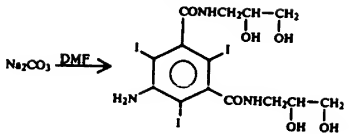
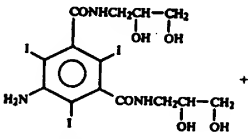


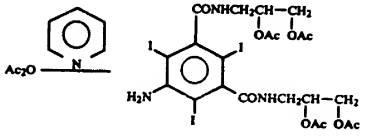
4

Pulverized 5-amino-2,4,6-triiodoisophthaloyl chloride 2 (4.35 Kg, 7.347 mol) was dissolved in DMF (6 L). The solution was cooled to 20° and Na_2CO_3 (2.33 Kg) was added; the temperature remained at 20°. To the reaction mixture was added, drop-wise, a solution of 3-amino-1,2-propanediol 3 (1.67 Kg, 22 mol) in 2.14 L of DMF with cooling (ice-bath) at 34°-35° over a period of 1.5 hour. After the addition, the reaction mixture was stirred at room temperature for 24 hours; the solid was filtered and washed with MeOH (3×500 ml). The filtrate and the MeOH wash were combined and evaporated under vacuum at 60°-63° (water bath) to give 4.5 L of a dark syrup. The warm syrup (50°-60°) was poured into a mixture of 45 L of water and 4 L of concentrated HCl with rapid stirring. The solution was stirred for 45 minutes, and evaporated under reduced pressure at 65°-70° (water-bath) to a volume of 28 L, washed with EtOAc (2×9 L) and further evaporated under reduced pressure at 65°-70° (water bath) to a volume of 12 L. The solution was diluted with 24 L of MeOH, seeded with an authentic sample of 4 (4-5 g) and stirred at room temperature for 2 days. Off-white solids precipitated during the stirring period. The solids were collected, washed with MeOH, suction-dried, and transferred to a tray and oven-dried at 70° for 24 hours to give the desired product 4 (2.582 Kg, 49.85% yield). The product showed one spot by tlc analysis (EtOAc/-MeOH/AcOH; 10/5/1). LC purity: 98.5% (peak height) (μC18, H_2O/CH_3CN; 60/40, flow 1 mL/min, retention time 3 minutes).

C. Preparation of 5-Amino-N,N'-bis(2,3-diacetoxypropyl)2,4,6-triiodoisophthalamide (5)



4



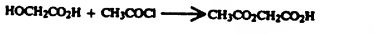
5

Compound 4 (2.58 Kg, 3.66 mol) was slurried in pyridine. Acetic anhydride (1.7 Kg, 16.65 mol) was added, drop-wise, to the slurry with stirring and cooling (ice-bath) over a period of 1.25 hours. The slurry temperature during this period was maintained at 33°–34°. After the addition the stirred slurry was allowed to cool to room temperature. During this time the slurry gradually became clear and the resulting solution was allowed to stir at room temperature for 17 hours.

The reaction solution (5.24 L) was diluted with EtOAc (10 L); ice water (7.32 L) was added and the mixture was stirred for 15 minutes. A mixture of ice water (7.32 L) and concentrated HCl (1.464 L) was added and the mixture was stirred for 45 minutes. The layers were separated (separation time 15 minutes) and the brown organic layer (bottom layer) was collected. The aqueous layer was extracted with EtOAc (2×5 L) and each time the organic layer (top layer) was collected. The organic layers were combined (25 L) and washed with the following solutions: 1. A mixture of water (3.66 L) and concentrated HCl (0.366 L); 2. A mixture of water (3.66 L) and concentrated HCl (0.18 L) and 3. 10% NaCl solution (4 L). The organic layer was then dried over anhydrous Na_2SO_4 (800 g) overnight. The solution was filtered and evaporated under reduced pressure at 60° (water bath) to give 5 as a yellow, glassy product. The product was then dried under vacuum at 60° for 13 hours, 3.21 kg (theory: 3.19 kg, >100% yield, due to the presence of HOAc).

The product showed one spot by tlc analysis ($EtOAc/CH_2Cl_2$; 30/20, Rf: 0.36); lc purity: 97–98%. (μC_{18}, H_2O/CH_3CN; 60/40, flow 1.0 mL/min, retention time 9.8 min); two minor peaks occurred before and one minor peak after the main peak.

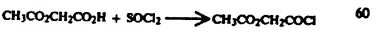
D. Preparation of Acetoxyacetic Acid (Acetylglycolic Acid) (7)



6 7

Acetyl chloride (778.3 g, 9.91 mol) was slowly (30 min.) added to glycolic acid (493 g; 6.48 mol) with cooling and stirring. The temperature was kept at 15°–25°. After the addition was complete, the mixture was stirred at room temperature for 0.5 hour at which time a violent expulsion of HCl gas occurred causing the reaction to set up solid. Toluene (1 L) was added, and the mixture was heated to 70° in order to dissolve the solid. The solvent was removed under reduced pressure resulting in an oil to which toluene (2 L) was added. After the mixture was allowed to stand overnight, the solids were collected, washed with toluene (1 L) and air-dried to give 568.75 g (74.3%) of 7, m.p. 65°–66.5° (lit. 67°–70°). The pmr spectrum was consistent with the assigned structure.

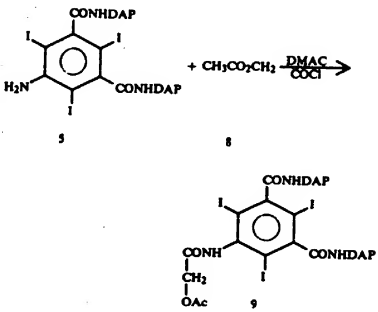
E. Preparation of Acetoxyacetyl Chloride (8)



7 8

The acetoxyacetic acid (568.75 g, 4.82 mol) and thionyl chloride (759.19 g, 6.38 mol) were combined and heated with stirring at 65°–70° for 1 hour. The solution was then heated 1 hour at 70°–75° and lastly 1 hour at 77° (reflux). The thionyl chloride was removed under reduced pressure and the residue was vacuum distilled. The fraction boiling at 53°–60° (12–15 mm) was collected giving 85.6% of 8. The ir spectrum was consistent with the assigned structure.

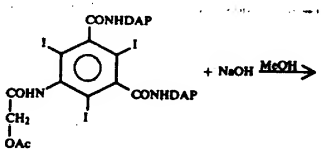
F. Preparation of 5-Acetoxyacetamido-N,N'-Bis(2,3-diacetoxypropyl)-2,4,6-triiodoisophthalamide (9)



DAP = $-CH_2CHOAcCH_2OAc$

Compound 5 (349.32 g, 0.4 mol) and DMAC (1050 ml) were combined. The stirred mixture was cooled to 5°. The acid chloride (163.85 g, 1.2 mol) was added slowly keeping the temperature at 5°–10°. When the addition was complete the reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. Water (36 ml) was added to the reaction mixture. The temperature rose to 48° and then began to fall. The mixture was added to water (5 L) which was extracted with ethyl acetate (4×1000 ml). The combined organic extracts were washed with 10% $NaHCO_3$ solution (2×1000 ml), water (1000 ml) dried over Na_2SO_4 and evaporated under reduced pressure to give 321.26 g (82.5%) of 9. The pmr spectrum was consistent with the assigned structure.

G. Preparation of N,N'-Bis(2,3-dihydroxypropyl)-5-glycolamido-2,4,6-triiodoisophthalamide (10)



DAP = $-CH_2CHOAcCH_2OAc$

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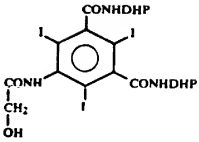
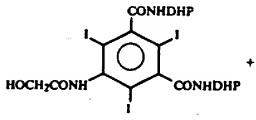


10

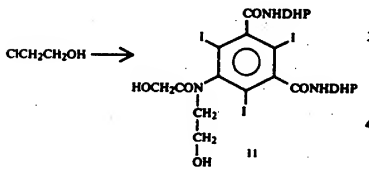
DHP = $-CH_2CHOHCH_2OH$

Compound 9 (321.26 g, 0.33 mol) and MeOH (1650 ml) were combined and stirred until all solids dissolved. To this solution was added 1 N NaOH (1650 ml, 1.65 mol). The mixture was stirred for 30 min; HCl (137.5 ml, 1.65 mol) was then added. The solution was evaporated under reduced pressure to give a residue which was carried on to the next step without purification.

H. Preparation of N,N'-Bis(2,3-dihydroxylpropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide (11)



10



11

DHP = $-CH_2CHOHCH_2OH$

The residue 10 (251.82 g, 0.33 mol; assume theory) was mixed with 1 N NaOH (412 ml, 0.412 mol). The mixture was stirred at room temperature until all solids dissolved, then the solution was stirred for 1 hour. 2-Chloroethanol (40.25 g, 0.5 mol) was added and stirring was continued for three days. To the mixture was added 1 N NaOH (330 ml, 0.33 mol); and after the mixture was stirred for 1 hour, 2-chloroethanol (32.2 g, 0.4 mol) was added. After three more days, another portion of 1 N NaOH (150 ml, 0.15 mol) was added. After being stirred 1 hour, a final quantity of 2-chloroethanol (16.1 g, 0.2 mol) was added. The solution was stirred overnight and then was evaporated to dryness under reduced pressure. The residue was triturated with MeOH (1 L) for 1 hour. The precipitated solids were filtered off and the mother liquor was concentrated in vacuo. The crude product was purified by preparative liquid chromatography to give 127 g (47.7%) of 11; m.p. 186°-198°; tlc ($CHCl_3$/MeOH/HOAc, 70/30/2; Merck silica gel plate)-one spot (Rf-0.51); lc (H_2O/THF: 99.75/0.25; Hibar-II, Lichrosorb RP-18,10 μm, 10°) -two components (chromatographic purity: 97.3%); the ir and pmr spectra were consistent with the assigned structure Cal. for $C_{18}H_{24}I_3N_3O_9$; C: 26.78, H: 3.00; I: 47.17; N: 5.21 Found; C: 26.47; H: 3.23; I: 46.83; N: 5.12.

EXAMPLE II

RADIOGRAPHIC OBSERVATIONS

A male mouse (23 g) was anesthetized with sodium pentobarbital (40 mg/kg, i.p.; Nembutal ®, Abbott Laboratories). The N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide prepared by method of Example 1, was administered at a dose of 10,000 mg I/kg (40% I solution) via a lateral tail vein of the mouse at a rate of 1 ml/minute. Whole body radiographs in the ventrodorsal position were taken immediately and 5 minutes after administration with opacification of the liver and cardiovascular and renal excretory systems.

A pentobarbital-anesthetized male rat (234 g) received an intracisternal injection of 137 mg I/kg (40% I solution) of the N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide, prepared by method of Example 1. A lateral radiograph of the head and thorax, obtained immediately after administration, demonstrated good visualization of the cisterna magna, basal cisterns, and cervical subarachnoid space.

EXAMPLE III

The following pharmacological studies were conducted on N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide (PRODUCT), prepared by the method of Example 1.

1. Acute Intravenous Toxicity in Mice

A solution of the PRODUCT (40% I) was injected into the lateral tail vein of young adult male and female Swiss mice at a rate of 1 ml/min. Following injections, the animals were observed for immediate reactions and then daily throughout a seven day observation period. Lethality data were as follows:

DOSE (mg I/kg)	DOSE (mg/kg)	NUMBER OF MORTALITIES/ NUMBER DOSED
18,500	39,220	0/8
20,000	42,400	5/8
21,500	45,580	10/10

Thus the LD_{50} value is probably about 20,000 mg I/kg.

2. Acute Intracisternal Toxicity in Rats

The technique described by Melartin, et al. (Invest. Radiol. 5: 13-21, 1970) was utilized to evaluate lethal effects of a solution of the PRODUCT after injection into cerebrospinal fluid at the cisterna magna. Young adult male Sprague Dawley rats were used. After dosing, the animals were housed individually and observed for immediate reactions and periodically for a two day observation period. The LD_{50} value was calculated by the method of Litchfield and Wilcoxin (J. Pharmacol. Exp. Therap. 96: 99-113, 1949) with the following results:

CONCENTRATION	LD_{50} (95% Confidence Limits)	
(mg I/kg)	mg I/kg	mg/kg
450	1,100	2,332

-continued

CONCENTRATION (mg I/kg)	LD_{50}/(95% Confidence Limits) mg I/kg	mg/kg
	(874–1,385)	(1,853–2,936)

3. Acute Intracisternal Neurotoxicity in the Dog

Three dogs (2 male, 1 female) were briefly anesthetized with thiopental sodium (20 mg/kg, iv., Nembutal ®, Abbott Laboratories) and single doses of 314 (1 dog) or 320 Mg I/kg (2 dogs) of the PRODUCT (50% I solution) were administered into cerebrospinal fluid at the cisterna magna. The dogs were observed thereafter for neurotoxicity. The animals displayed moderate CNS depression but no signs of convulsive or preconvulsive behavior.

4. Intracoronary Cardiotoxicity in the Isolated Perfused Rabbit Heart

Four female New Zealand albino rabbits (3.4–4.3 kg) were employed for this study. Rabbits were sacrificed by cervical dislocation, the hearts excised and coronary perfusion was performed via the aortic root using an oxygenated physiological salt solution heated to 37° C. A solution of PRODUCT (37% I) was warmed to 37° C. and intracoronary bolus injections (4 ml) were made via a sidearm of the perfusion apparatus. The heart rate (HR), contractile force (CF), and electrocardiogram were recorded and results were as follows:

Mean % Change from Control HR and CF - at Various Times after PRODUCT Administration

DOSE (mg I/Heart		0–15 sec	15–30 sec	1 min	2 min	4 min.	Arrythmias Observed
1,480	HR	−5	5	3	3	−2	None
	CF	49	48	62	2	−36	

What is claimed:

1. N,N'-Bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide.

2. A radiological composition containing N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)-glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

3. In a method for X-ray visualization wherein a radiological composition containing an X-ray contrast agent in a pharmaceutically acceptable radiological vehicle is injected in a sufficient amount to provide adequate visualization and thereafter X-ray visualization carried out, the improvement comprising or utilizing as the radiological composition a composition containing N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.

* * * * *

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The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PAT NO NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	EXT YR	SML ENT	ST.
1	4,396,598	170	225	-	06/396,382	08/02/83	01/11/83	04	NO	PR

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

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Beiliegend finden Sie unsere Überweisung zur Zahlung der unten aufgeführten fälligen Jahresgebühren.

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Number Numéro Nummer	Patentee Titulaire Inhaber	Due Date Echéance Fälligkeit	Tax	Fee/Montant/Betrag US $	Fine/Surtaxe/Zuschlag US $	XXXXXXXXXX Workcon Charge XXXXXXXXXX SERIAL NO	Total US $
4395943	ESRO AG	02/02/87	04	225.00		06/304034	225.00
PAID 4396017 (16)	VICKERS LTD	02/02/87	04	225.00		06/228678	225.00
4396165	ESSEX GROUP INC	02/02/87	04	225.00		06/325525	225.00
4396398	SECRETARY OF STATE FOR DEFENCE	02/02/87	04	225.00		06/305736	225.00
4396470	VICKERS PLC	02/02/87	04	225.00		06/349194	225.00
4396592	MALLINCKRODT INC	02/02/87	04	225.00		06/338382	225.00
4396673	ICI LTD	02/02/87	04	225.00		06/289731	225.00
4396756	IMPERIAL CHEMICAL INDUSTRIES PLC	02/02/87	04	225.00		06/367613	225.00
4396759	SCHERING AG	02/02/87	04	225.00		06/381209	225.00
4397023	UNITED TECHNOLOGIES	02/02/87	04	225.00		06/317678	225.00
4397093	ROLLS-ROYCE LTD & RENISHAW ELECTRICAL	09/02/87	04	450.00		06/614502	450.00
					Page Total	US $	2700.00

970 /27/87 4396759 2 170 225.00 CK

Regd Office as Company Address
Regd in London No. 1085809
VAT Reg No. 158 3231 69
Directors: J.J. Dennemeyer (USA)
M.C. Dennemeyer (USA)

Bankers: Lloyds Bank Plc
Overseas Branch Manchester
Accounts:
£ No. 0183826
US $ No. 11144529
F Mks No. 37002848
DM No. 23044814
S Frs No. 24006010
Yen No. 35006528
N Fls No. 26016420

#2

Mallinckrodt, Inc.

675 McDONNELL BLVD. • P.O. BOX 5840 • ST. LOUIS, MO. 63134 • (314) 895-2000

December 20, 1985

Food and Drug Administration
Department of Health and Human Services
Center for Drugs and Biologics
Division of Oncology and Radiopharmaceutical
Drug Products, HFN #150
Attn: Document Control Room 9B-23
5600 Fishers Lane
Rockville, MD 20857

Ref: Original IND for MP-328

Gentlemen:

Enclosed is an original Investigational New Drug submission providing for the clinical investigation of an iodinated radiopaque agent with the code name of MP-328. Mallinckrodt has submitted the name Iovisatrol to the United States Adopted Names Council as the established name for MP-328, but it has not yet been approved. MP-328 will be studied for the indications of coronary arteriography, cerebral angiography, peripheral arteriography, visceral arteriography, head CT, body CT, intraarterial digital subtraction angiography, intravenous digital subtraction angiography, pediatric angiocardiography, urography and venography.

Sincerely yours,

David E. Brown

David E. Brown
Sr. Regulatory Affairs Associate

DEB:bh

MP328/C(1)

Mallinckrodt

EXHIBIT
D
4,396,598

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

#3

Food and Drug Administration
Rockville MD 20857

JAN 2 1986

IND 27630

Mallinckrodt, Inc.
P.O. Box 5840
675 McDonnell Boulevard
St. Louis, MO. 63134

Attention: David E. Braun, Sr. Regulatory Affairs Associate

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 27,630

Sponsor: Mallinckrodt, Inc.

Name of Drug: MP-328

Date of Submission: 12-20-85

Date of Receipt: 12-23-85

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

FORM FDA 3228a (6/82)

5A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-710

AUG 19 1987

Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, Missouri 63134

Attention: Niles B. Ross
Senior Regulatory Affairs Associate

Dear Mr. Ross:

We have received your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ioversol Injection (MP-328)
Date of Application:	June 25, 1987
Date of Receipt:	June 26, 1987
Our Reference Number:	NDA 19-710

Unless we find the application unacceptable for filing, the filing date will be August 24, 1987 and the due date, December 22, 1987.

Under 21 CFR 314.102(c), and in accordance with the policy described in the Center for Drugs and Biologics Staff Manual Guide CDB 4820.6, you may request an informal conference with this division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report or if you have any questions concerning this NDA, please contact Mr. Robert L. West, Consumer Safety Officer at (301) 443-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Product
Office of Drug Research and Revi
Center for Drugs and Biologics

AUG 20 1987
REGULATORY AFFAIRS

EXHIBIT E
4396, 578

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-710

DEC 30 1988

Mallinckrodt, Inc.
675 McDonnell Boulevard
P.O. Box 5840
St. Louis, Missouri 63134

Attention: Niles B. Ross
Senior Regulatory Affairs Associate

Dear Mr. Ross:

Reference is made to your new drug application dated June 25, 1987 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the diagnostic radiocontrast agents Optiray-160 (ioversol injection 34%), Optiray-240 (ioversol injection 51%) and Optiray-320 (ioversol injection 68%).

We acknowledge the receipt of your May 14, 1987 presubmission of chemistry, manufacturing and controls information and your amendments dated September 9, October 16 and December 7, 1987; February 17, April 15, May 16, July 21, August 15, October 19, October 31, November 16, November 22, December 8, December 12 and December 19, 1988. We also acknowledge the receipt of your communications dated March 14, April 26, July 18, November 2 and November 10, 1988 and refer to the meetings held between representatives of Mallinckrodt, Inc. and this Administration on October 15 and December 10, 1987 and December 2, 1988. In addition, we acknowledge the receipt of your December 12, 1988 proposed introductory promotional and advertising campaign.

We have completed the review of this application as amended including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted on June 25, 1987 and amended on December 19, 1988. Accordingly, the application is approved effective as of the date of this letter.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed. In such a case, the policy of the Center for Drug Evaluation and Research is to proceed with approval. We expect your cooperation to help resolve expeditiously any problems that may occur with respect to validation.

The final printed labeling (FPL) must be identical to the draft labeling as amended on December 19, 1988. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as possible. Seven of the copies should be individually mounted on heavy weight paper or similar material. This submission should be designated for administrative purposes as "FPL for approved NDA 19-710." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

#4

MP-328

DLL #	DATE	DESCRIPTION
	8/8/85	Letter (MI/FDA) requesting a meeting regarding MP-328.
	8/15/85	Telephone Call Report (FDA/MI) from Mr. West with the following info: the meeting will be held 9/17/85, Conference Room H on the 3rd Floor.
	9/11/85	Letter (MI/FDA) to Mr. West informing him of some changes in MI's proposed clinical plan on a new non-ionic contrast agent (MP-328) and suggesting that an additional item be added to the agenda for discussion, prior to the 9/17 meeting.
pre-filing activities	9/17/85	Memorandum of a Meeting (FDA/MI). Minutes of the meeting held at FDA 9/17/85. Topic: Review of a Proposed Clinical Program for MP-328, a New Non-ionic Contrast Medium.

ROLL #	DATE	DESCRIPTION
Filed	12/20/85	ORIGINAL NOTIFICATION: MK/FDA. MK has submitted the name IOVISATROL to the USANC as the established name for MP-328, but it has not yet been approved. MP-328 will be studied for the indications of coronary arteriography, cerebral angiography, peripheral arteriography, visceral arteriography, head CT, body CT, intraarterial digital subtraction angiography, intravenous digital subtraction angiography, pediatric angiocardiography, urography and venography.
	12/26/85	Telephone Call Report: to FDA - IND received today.
	1/02/86	Letter:FDA/MK. Notifies MK of receipt of IND submitted 12/20/85 and received by FDA on 12/23/85. IND number assigned 27,630.
	2/11 and 2/12	Telephone Call from Bob West to EMA asking if we started clinical trials. EMA stated we have. Mr. West suggested that Dr. Nissel might have some questions and has not finished his review.
	2/13/86	Letter: to FDA requesting a meeting on many subjects and stating that EMA will be available to Dr. Nissel for any questions on the clinical program.
	2/18/86	Telephone Call Report from FDA to K. McElvaney, with some "touchup" suggestions on protocols for Dr. Drayer, Dr. Osborn, Dr. Bettman, Mr. Meyerovitz.
	2/26/86	Amendment to add Dr. Karl Theisen study in Munich, Germany. Postal receipt dated 2/28/86.
	3/10/86	Telephone Call Report (MI/FDA). Discussed with Mr. West about a possible meeting with Dr. Nissel the first week in April to respond to any questions Dr. Nissel might have relating to the MP-328 program.
	3/24/86	Revision (MK/FDA). Revision to Protocol 3A, Study #207 and addition of study Protocol 7A, Study #210, Dr. Murphy. PR dated 3/27/86.
	3/25/86	Letter (MI/FDA) to confirm meeting with Dr. Nissel on Tuesday, April 1, 1986 to answer any questions Dr. Nissel might have relating to MP-328 clinical program. Acknowledgement dated 3/26/86.
	4/11/86	Letter (MK/FDA). Dr. Murphy's curriculum vitae submitted for Protocol 7A (Study 210). PR dated 4/15/86.
	4/11/86	Amendment. Addition of Dr. Heystraten, Study 228, Protocol 27,630-4B, comparing MP-328 32% to Omnipaque-300 (Iohexol) in peripheral visceral arteriography. PR dated 4/15/86.

ROLL #	DATE	DESCRIPTION
	4/11/86	Amendment to IND to provide for alternate manufacturing method by [redacted] "diester" route. In addition, tentative specifications for MP-328 new drug substance (A2180-R05) is revised to provide for rabbit pyrogen test in place of endotoxen text. PR dated 4/16/86.
	4/18/86	Amendment (MK/FDA). Adds study #212 conducted by Dr. J. W. Goethe, Prof. Dr. Jurgen Kollath and Jurgen Scherberich, University at Frankfurt am Main, Germany. "A Double Blind Study Comparing the Safety, Tolerance and Efficacy of MP-328 and Omnipaque in Peripheral and Visceral Arteriography. PR dated 4/21/86.
	4/28/86	Amendment (MK/FDA). Amendment to add 1) Dr. Philip Gishen, Kings Hospital, London, England, as a principal investigator for a "Double-Blind Study Comparing the Safety and Efficacy of MP 328 (32%) and Niopam 370 (Iopamidol) in Selected Coronary Arteriography, 2) A Double-Blind Clinical Study Comparing the Safety, Tolerance and Efficacy of MP 328 (24%) and Omnipaque 240 (Iohexol) in Ascending Phlebography conducted at Northwick Park Hospital, Middlesex, England. PR 4/29/86.
	4/29/86	Amendment (MK/FDA). 1) Revised CV for Dr. Drayer (Study 205), 2) Protocol for Study #209 (Drs. Gado, Sartor, Hodges), 3) Protocol for Study 232 (Dr. Hirshfeld. PR dated 5/1/86.
	5/1/86	Letter (MK/FDA). Refers to 2/26/86 amendment for Dr. Karl Theisen. Submitted CV's for Drs. Vogler, Kotzur, Haufe and Zwehl as co-investigator PR dated 5/6/86.
	5/2/86	Amendment (MK/FDA). Submission of Protocol, case report forms and CV for principal investigator for Study 216, Dr. Ayres at St. Thomas Hospital, London; Study 222, Jean-Claude Gaux, Brossais Hospital, Paris, France; J. L. Lamarque, Study 223 at Lapeyronie, Montpellier, Cedex, France; Study #225, J. Ecoiffier at Hotal Dieu de Paris, Paris, France. PR dated 5/6/86.
	6/19/86	Letter (MK/FDA). Corrects page 10.285 in Study 208, Protocol 4A, Dr. Michael Meyerovitz, page 7. Postal receipt dated 6/24/86.
	6/30/86	Amendment (MK/FDA). Add European Study 213, Dr. Erich Klotz; Study 224, Dr. Jean Tongio; Study 226, Dr. Roland Tauber; Study 227, Dr. G. J. Vielvoye; Study 238, Dr. Van Seyen. PR dated 7/3/86.
	7/21/86	Letter (MI/FDA) adding co-investigator Valerie Mandell, M.D. to Studies 207 and 208, and enclosing cover sheet to each protocol referencing the addition and the curriculum vitae for Valerie Mandell. PR dated 7/24/86.
	7/28/86	Amendment (MI/FDA). Study 206, Protocol 27,630-2A, change in patient status. PR dated 8/1/86.
	7/23/86	Telephone Call Report (MI/FDA). MI called Mr. West to discuss a pre-Phase III MP-328 meeting with the FDA. This meeting had originally been agreed upon for August, 1986. MI explained to Mr. West due to delayed initiation of the European studies, there would be limited data available for a meeting at this time and suggested postponing the meeting until [redacted] November or December. Mr. West indicated this would be agreeable to the Agency.

OLL #	DATE	DESCRIPTION
	8/14/86	Letter from FDA summarizing our IND protocols and listing 9 agreements between FDA and K. McElvany. FDA also makes two clinical recommendations (name change of proposed name; change in maximum dose for Study 214, and include D. Lankin's C.V.) and 3 pharmacology recommendations (perform cell transformation and DNA repair test, further toxicity studies on MP-429, keeping dose low in early clinical trials for selective coronary arteriography).
	8/27/86	Amendment (MK/FDA). Add studies 241 (Protocol 27,630-4B), Dr. Schwarten; Studies 239 (Protocol 27,630-14) Dr. Levy. PR dated 9/2/86.
	9/3/86	Telephone Call Report (MI/FDA) to FDA physiologist Sidney Stolzenberg concerning FDA letter of August 14, 1986. Pharmacology question 1 - we will not have to do cell transformation assay and DNA repair test as recommended. Pharmacology question 2 - we will not have to do pharmocokinetic studies on possible contaminants as requested.
	9/23/86	Amendment (MI/FDA). Protocol 27,630-13 (Study 240). Principal investigator is Dr. Franklin Miller, U. of Utah Medical Center, Salt Lake City, UT. PR received.
	10/1/86	Letter (MI/FDA) in reply to questions in FDA's letter of August 14, 1986. PR dated 10/6/86.
	10/29/86	Amendment (MI/FDA) to add the following studies. For each study listed, MI attached the protocol, case report forms and C.V. for principal investigator and co-investigator for Study No. 219. (1) Study No. 218 conducted by Prof. W.S.C. Hare at Royal Melbourne Hospital, Melbourne, Australia; (2) Study No. 219, conducted by Prof. W.S.C. Hare (Prinicpal Investigator) & Dr. K. Thompson (Co-investigator), at Royal Melbourne Hospital, Melbourne, Australia; (3) Study 220, conducted by Prof. F. J. Palmer at Prince Henry Hospital, Little Bay, Australia; and (4) Study 230, conducted by Prof. M. R. Sage at Flinder MedicalCentre, Bedford Park, South Australia.
	11/4/86	Amendment (MI/FDA). Study 230 to add Dr. G. T. Fon as an additional co-investigator. PR dated 11/10/86.
	11/12/86	Amendment (MI/FDA). Amends Protocol 27,630-3A for Study 207 for inclusion of diabetic patients. PR received.
	11/12/86	Amendment (MI/FDA). Adds Study #244, Protocol 27,630-18, conducted by Dr. Gary Becker, co-investigators Dr. Justin Wass, Dro Kenyon Kopecky at Indiana University School of Medicine, University Hospital, Indianapolis, IN. PR dated 11/17/86.
	11/14/86	Amendment (MI/FDA). Adds Study 249, Protocol 27,630-1B, conducted by Dr. Akira Shishido, Hosen Clinic, Tokyo, Japan. PR received
	11/20/86	Amendment (MI/FDA). Provides for IVP study by Dr. Winfield, Vanderbilt Univ., Nashville, Tennesse. PR dated 11/25/86.
	11/24/86	Amendment (MI/FDA). Adds Dr. R. L. Philips to Study 220, conducted at Prince Henry Hospital. PR dated 12/1/86.

ROLL #	DATE	DESCRIPTION
	12/10/86	Amendment (MI/FDA). Adds Study 246, Dr. Heggelman and Dr. Molewaterplein Rotterdam, The Netherlands. PR Received.
	12/12/86	Amendment (MI/FDA). Adds Study 236, Dr. Ruth Ramsey, St. Luke's Medical Center, Chicago, IL. PR received.
	12/15/86	Amendment (MI/FDA). Interim Safety Summary and Urography Study Medical Report conducted by Dr. Spataro in which the efficacy, tolerance and safety of ioversol and Renografin-60 were compared.
	12/17/86	Letter (FDA/MI) stating they have completed their review of the manufacturing and controls portion of the IND and have concluded that it is reasonably safe to proceed with the studies as proposed. FDA also requested additional chemistry information to which MI should respond prior to initiating expanded Phase III studies.
	12/17/86	Telephone Call Report (MI/FDA) to Bob West to confirm that he had receive our 12/15/86 submission which consisted of the Interim Safety Update & Urography Study Report. Mr. West had the material and requested that we send an additional four copies for review within the Division. The pre-NDA meeting is tentatively scheduled for January 13, 1987. Mr. West asked that MI provide a more detailed agenda and apprise him of any needs for audio-visual equipment. MI asked that Dr. Wood be included in the meeting in that we propose to discuss the merits of an early manufacturing and chemistry submission, as well as the possible benefits of an electronic-NDA. MI agreed to follow-up with Mr. West to provide the additional details concerning our meeting and confirm the date and time.
	12/19/86	Amendment (MI/FDA). Adds Study 250, Dr. John Hirshfeld, University of Pennsylvania Hospital, Philadelphia, PA. Postal receipt recieved.
	1/2/87	Telephone Call Report (FDA/MI) from Mr. West with the following tentative dates for the meeting: Pre-NDA MP-328, Thursday, 1/22/87, 10:00 a.m. Mr. West was informed that MI would call to confirm the date and time.
	1/6/87	Telephone Call Report (MI/FDA) to Mr. West to confirm the schedule for the MP-328 pre-NDA meeting, 1/22/87, 10:00 a.m. held in 14B-45 and last 1 1/2 hrs. Mr. West estimated approximately 12 people from FDA would attend. Mr. West is not scheduled to be in the office that week and expects that Mark Anderson will attend the meeting. MI also discussed the proposed agenda with Mr. West/
	1/15/87	Letter (FDA/MI) with requests & recommendations regarding protocols submitted 8/27 and 9/23/86.
	1/15/87	Letter (FDA/MI) with requests & recommendations regarding our 11/14/86 submission for Study No. 249.

DATE	DESCRIPTION
1/15/87	Telephone Call Report (MI/FDA) to Mr. West asking if it would be possible to meet separately with Dr. Wood and the reviewing chemist on January 22nd to explore questions that had been raised in the IND chemistry letter. MI explained that the focus of our pre-NDA meeting that day would be to review the clinical data and we did not feel there would be adequate time to discuss the chemistry questions as well during the hour and a half allotted for our meeting. MI agreed to contact him 1/16 to determine whether a separate meeting was possible.
1/16/87	Telephone Call Report (MI/FDA) to Mr. West to see if he was successful in scheduling a separate meeting to pursue the IND chemistry questions. A meeting has been arranged with Drs. Wood, Sieczkowski and possibly Jerussi for 12:45 to 1:30 P.M., 1/22/87. MI told Mr. West we would limit our participation to three or four people.
1/26/87	Annual Report (MI/FDA). Includes Ioversol Clinical Program and Interim Safety Summary; Study Report - Pharmacodynamics of MP 328 in the Dog Isolated Perfused Hindquarter; Specifications for MP 328 (Ioversol); [redacted]%) (51%) (68%); Standard Method, Standard Procedure, Stability Studies, Synthesis of MP 328.
1/29/87	Minutes of the 1/22/87 Pre-NDA meeting with personnel from the Division of Oncology and Radiopharmaceutical Drug Products.
1/30/87	Meeting Minutes (MI/FDA). Regarding meeting held at FDA on 1/23/87 regarding FDA's letter of 12/17/86. Desk copy sent to M. Anderson. PRs dated 2/3/87.
2/5/87	Letter (MI/FDA). Response to 2 FDA letters (1/15/87) discussing protocols for Studies 239, 241 and 249. PR dated 2/11/87.
2/17/87	Meeting Minutes (FDA/MI). FDA's meeting minutes for the 1/22/87 pre-NDA meeting held at FDA.

MP-328
IND 27,630

ROLL #	DATE	DESCRIPTION
	3/5/87	Response to Chemistry Questions: (MK/FDA) FDA letter dated 12/17/ regarding manufacturing and controls section. Postal Receipt 3/10/87 appended.
	3/13/87	Letter (MK/FDA) Withdraws Study #227 Protocol 27,630-28, Dr. G. J. Vielvoye, Univ. of Leiden, Leiden, The Netherlands. Postal receipt 3/19/87.
	4/15/87	Amendment: (MK/FDA) Adds coinvestigator Alan J. Kaufman, M.D. to study No. 247, Protocol 27,630-10, conducted by Alan C. Winfield, M.D., Vanderbilt University, Nashville, TN. Postal receipt 4/22/87.
	4/21/87	Letter (FDA/MK) questioning our 10/1/86 answer to FDA's 8/14/86 letter regarding Ames and acute toxicity testing. FDA recommends further mutagenicity testing on MP-429 and MP-104.
	5/5/87	Telephone Call Report: (FDA/MK) IND Question on Pharmacology relating to genetic toxicity testing of MP-104 and MP-429
	5/8/87	Letter (MK/FDA) Responds to FDA letter of 4/21/87 regarding mutagenicity testing of MP-429 and MP-104.
	5/12/87	Telephone Call Report (FDA/MK) Inquiring if Dr. Sieckowski would be assigned the MP-328 NDA. He said he had not heard officially, but he expects to get the NDA.
	7/22/87	Amendment (MI/FDA) Provides for an IVP study 234 by Dr. Robert Graham, Toronto, Canada and a Selective Coronary Arteriography Study 234 by Dr. Richard Davies, Ottawa, Canada.

11#.	Date	Description
	10/30/87	Letter: MI/FDA - Proposed clinical plan for 30/35%, submitted to Dr. Jones for comment. P.R. dated 11/2/87.
	11/24/87	Request for Mtg. to review clinical plan for 30 and 35% PR dated 11/30/87.
	12/3/87	Minutes of Mtg. with FDA (FDA/MI) to discuss preposed clinical plan for 30 and 35% formulations.
	12/23/87	Letter (MI/FDA) Sending minutes of 12/3 meeting reviewing MI's proposed clinical study plan for ioversol formulations containing 30 & 35% iodine. PR dated 12/28/87.
	1/20/88	Amendment (MI/FDA) Includes; 1 study 328-36, and open label non-comparative clinical study to evaluate the safety, tolerance and efficacy of ioversol-320 in cerebral angiography, by Professor Yutaka Kuru at Juntendo University Tokyo, Japan, and 2. Study 328-20, an open label non-comparative clincial study to evaluate the safety, tolerance and efficacy of ioversol-320 in contrast enhanced cranial computed tomographic scanning, by Dr. Hirotoshi Sumie at Juntendo University, Tokyo, Japan.
	1/28/88	Amendment (MI/FDA) To provide for 30% and 35%. Includes chemistry for drug substance and drug product, labeling and seven clinical protocols; Study 271, IVDSA (Dr. Camplbell), Study 272, Head CT (Dr. Ramsey), Study 273 body CT (Dr. McLennan), Study 274 body CT (Dr. Kopecky), Study 276 Urography (Dr. Katzberg), Study 277 Urography (Dr. McClennan), Study 278 Cerebral Angiography (Dr. Osborn).
	2/2/88	Letter (MK/FDA) Clarifies our intentions regarding Japanese studies. Also compares differences between Japanese and US protocols. Acknowledgement Letter 2-3-88.
	2/8/88	Annual Report (MI #001/FDA) Includes summaries of all clinical studies list of preclinical studies submitted to the NDA, current specifications and methods and stability data. Postal receipt but with no date stamped.
	2/12/88	Telephone Call Report (FDA/MK) Dr. Ju to MI. Listed differences between new protocols and those previously submitted. Insure sufficient number of patients have BUN and creatinines measured. Do not submit 30% and 35% data until all medical issues in NDA are completed. Don't submit pediatric protocols until MI consults with division; do not initiate study until protocol is reviewed.
	2/23/88	Amendment (MI/FDA) Provides protocol for 16 Japanese studies.
	2/24/88	Amendment (MI/FDA) To provide Study 275: A double-blind study comparing the safety, tolerance and efficacy of ioversol-350 and Omnipaque-350 (Iohexol) in peripheral and visceral arteriography, by Dr. Palestrant of Phoenix A2. A list of differences between this protocol and Study 208 in the NDA is supplied. Postal receipt received 3/1/88.

Roll #	Date	Description
	3/2/88	Telephone Call Report (FDA/MI) Dr. Ju asking MI to increase the number of patients for various studies in the 30 and 35% amendment of 1/28/88.
	3/9/88	Telephone Call Report (FDA/MI) Bob West, FDA, called regarding the 1/28/88 amendment on 30% and 35% ioversol. (1) Provide BUN and creatinine 72-hours post-injection. (2) Add more patients to the studies to establish a statistically significant number. (3) Use the NDA neurologic examination report in cerebral angiography studies. (4) Establish norms for all measurable criteria, and consider values exceeding the norms as adverse reactions.
	3/10/88	Letter (MI/FDA) To Dr. Ju responding to his 2/12/88 phone call. MI gives FDA the differences between each protocol in the 30 and 35% amendment to the IND and protocols for similar studies in the NDA. Postal receipt received 3/16/88.
	3/11/88	Amendment (MI/FDA) Amend IND to add Amendment 004 for an open-label study with ioversol-350 for contrast enhanced cranial computer tomographic scanning, conducted by Marcus Hedgcock, M.D., of San Francisco, CA. Postal receipt received 3/17/88.
	3/21/88	Amendment 5 (MI/FDA) Provides for Study 280, an open-label study with ioversol-300 for contrast enchanced body computed tomographic scanning by Lincoln Berland, M.D., of Birmingham, AL. Postal receipt received 3/24/88.
	3/24/88	Telephone Call Report (FDA/MI) from Dr. Ju. He requested that we compare new protocols to the IND both to the original protocols in the NDA as well as to previously submitted protocols which are similar.
	3/24/88	Telephone Call Report (FDA/MI) from Dr. Ju. He is concerned that the maximum amount of dosage allowed in some ioversol-350 protocols is 250 mL, equivalent to 87.5 gm iodine. He feels this should be cut back to 225 mL. The 225 mL would be consistent with the maximum iodine dose in the ioversol-320 NDA.
	4/5/88	Amendment 006 (MI/FDA) Provides study 295 by Dr. Maravilla of Seattle, An open label non-comparative clinical study to evaluate the safety, tolerance and efficacy of ioversol-350 in contrast enhanced cranial computed tomographic scanning. This protocol is the same as Study 281 (Dr. Hedgecock), submitted 3/11/88. P.R. dated ----(no date noted).
	4/8/88	Telephone Call Report (FDA/MI) - With Marty James and FDA's statistician Dr. David Hoberman. If MI intends to claim superiority of ioversol relative to other products, our clinical protocols must address the appropriate sample size needed to obtain statistical relevance.
	4/7/88 Amend. 007	Amendment 007 (MI/FDA) Makes a correction to amendment. This amendment corrects the comparison between the studies, correctly comparing Study 244 in the NDA (Becker) with Study 280 (Berland) in the IND. Postal Receipt dated 4/14/88

Roll #	Date	Description
	5/20/88	Letter (MI/FDA) Plans for collecting laboratory data in pediatric studies. P.R. dated 5/26/88
	5/23/88	Telephone Call Report (FDA/MI) from Dr. Ju suggests that both heat and pain (not only just heat) be evaluated in 35% coronary patients (see study 294, Dr. McGauhey), to confirm to the 32% studies in the NDA.
	5/24/88	Amendment (MI/FDA) Amendment 014 provides for Study 292 comparing ioversol-300 and omnipaque-300 (ioherol) intravenous excretory urography by Dr. Thompson of Minneapolis. P.R. dated 6/1/88
	5/25/88	Amendment 016 provides 6 French studies at 35% concentration in IV-DSA, head CT, body CT, urography, coronary arteriography, venography. Postal Receipt dated 6/3/88.
	6/2/88	Amendment 017 (MI/FDA) provides for 6 French studies: Dr. Palmers, Head CT; Dr. Carcy, Venography; Dr. Lacombe, IV-DSA; Dr. Vasile, Body CT; Dr. Pinet, Urography; Dr. Elke, Urography. All use ioversol-350. Postal Receipt dated 6/7/88.
	6/2/88	Telephone Call Report (FDA/MI) from Dr. Ju discusses MI's plan for pediatric studies. MI should not begin pediatric studies until we receive a formal letter which may (pending Dr.Jones approval) make a number of points: inadequate hematology profile; better follow-up on BUN and creatinine; postpone 35% studies until the 32% application is approved, or until there is sufficient 30% safety data.
	6/2/88	Telephone Call Report (FDA/MI) Bob West that we more explicitly state in protocols that the reader of the X-ray is blinded.
	6/6/88	Amendment 018 (MI/FDA) provides for an open label body CT study in Japan. P.R. dated 6/8/88.
	6/8/88	Amendment 019 (MI/FDA) provides for comparing ioversol-300 and Isovue-300 in peripheral arteriography by Drs. Martin, Casarella & Alspaugh at Emory University, Atlanta, GA P.R. dated 6/13/88.
	6/10/88	Amendment 020 (MI/FDA) provides for two studies in Amsterdam. Study 301 for IVDSA compares ioversol-350 and Omnipaque-350 by Dr. Agenant. Study 301 is the same as 284 (amendment 008, 4/13/88) except that 284 uses 30% drugs. Study 302 for body CT uses ioversol-300 in an open-label study by Dr. Verbeeten of Amsterdam. Study 302 is exactlythe same as Study 280 (amendment 005, 3/21/88) thus no protocol is submitted. PR dated 6/21/88.

ROLL #	DATE	DESCRIPTION
	6/8/88	Letter (FDA/MI) Questions re neurological evaluation of patients in ioversol-300 studies
	7/6/88	Telephone Call Report (MI/FDA) regarding FDA requirements for pediatric studies on 30/35%.
	7/21/88	Letter (MI/FDA) D. Lankin to Dr. Jones - General 30 and 35% ioversol clinical studies. The collection of neurological data in studies #278 and 298 and pediatric studies.
	8/10/88	Telephone Call Report (MI/FDA) follow-up of Lankin's 7/21/88 letter.
	8/15/88	Letter (MI/FDA) Commitment to stop pediatric studies if 72 hr. BUN/Creatinine values are high. Postal Receipt dated 8/25/88
	8/25/88	Amendment 021 adds investigator Marvin Goldberg to study 292 originally submitted as Amendment 014 on 5/24/88. Postal Receipt received 8/30/88.
	9/21/88	Amendment 022 provides for a pediatric open label study using ioversol-300 for a pediatric study for intra-arterial digital substraction angiography. PR received 9/26/88.
	10/3/88	Amendment 023 provides for an open-label study using ioversol-300 in pediatric intravenous excretory urography by Dr. Schumacher in Germany. PR received dated 10/12/88.
	9/21/88	Protocols (MI/FDA) Two protocols for pediatric patients sent to Dr. Ju. PR received 10/5/88.
	10/20/88	Letter (FDA/MI) Confirming agreements on pediatric studies and 72 hr BUN/Creatinine follow-up.
	1/5/89	Amendment 024 (MI/FDA) revises protocol for study 301 (Amendment 020,6/10/88, Dr. Agenant of Amsterdam) by eliminating lab studies and cutting patients from 80 to 60.

#5
See 5A

Pre-filing activities

DATE	DESCRIPTION
12/17/86	TELEPHONE CALL REPORT (MI/FDA) Bob West confirmed he had rec'd our 12/15/86 submission. Suggested pre-NDA meeting be scheduled for week of Jan. 12.
1/2/87	Telephone Call Report(FDA/MI) Gave tentative dates for Pre-NDA meeting.
1/6/87	Telephone Call Report (MI/FDA) Confirmed schedule for Pre-NDA meeting
1/15/87	Telephone Call Report (MI/FDA) Called to ask if MI could meet separately with Dr. Wood & reviewing chemist to explore questions raised in the IND chemistry letter.
1/29/87	MI's minutes of Ioversol Pre-NDA Meeting, 1/22/87
1/30/87	Letter (MI/FDA) Forwarding MI's minutes of meeting on 1/23/87 re FDA's letter of 12/17/86. Postal receipt 2/3/87.
2/5/87	Telephone Call Report (MI/FDA) Called Dr. Palmer to follow-up on discussion re the feasibility of submitting the manufacturing and chemistry portion of NDA on 5/15/87 followed by 7/1/87 filing of full NDA. Mr. West stated they would be happy to receive in advance.
2/17/87	Meeting Minutes (FDA/MI) FDA's meeting minutes for the 1/22/87 pre-NDA meeting held at FDA.
4/8/87	Telephone Call Report (MI/FDA) FDA requests advance notice of shipping NDAs or supplements of greater than 50 volumes. They will assign NDA numbers in advance of shipments (not DMFs). The NDA number for ioversol sterile solution is 19-710. Estimated dates for arrival at document control are May 15-30. We are not held to these dates.

"Pre-filing" of NDA

5/14/87 Chemistry Pre-Submission Ioversol - NDA 19-710 Volumes 1 of 3
2 of 3, 3 of 3

5/15/87 Telephone Call Report (MK/FDA) Called Bob West to advise that the advanced chemistry submission will be arriving at FDA's control document room today, May 15, 1987. The drug substance portion will arrive 5/18/87.

5/28/87 Telephone Call Report (FDA/MK) Dr. Sieczkowski expressed concern about the quantity of silicone delivered from the standpoint of chemistry and toxicology. Dr. Sieczkowski felt our two problems with syringes will be silicone and microbiology. Dr. Sieźkowski has not heard officially about Ioversol, but is pretty sure he will be getting the NDA.

filing

6/3/87 Telephone Call Report (FDA/MK) Ioversol NDA prechemistry submission was received.

Actual NDA

6/8/87 Letter:(FDA/MK).Acknowledgement letter acknowledging receipt of chemistry pre-submission (5/14/87).

6/25/87 ORIGINAL SUBMISSION: MK/FDA.

7/7/87 Letter(MK/FDA). Desk copy of DMF 6972 was sent to reviewer to reference in NDA review.

7/31/87 Telephone Call Report:(MK/FDA). 90-Day NDA conference.

7/31/87 Telephone Call Report: (MK/FDA) Discussed meeting dates to "walk FDA through the NDA".

8/5/87 Telephone Call Report: (MK/FDA). Dr. Jones requested two additional desk copies of Volume 2.15.

8/6/87 Letter:(MK/FDA).Requests 90-day post-NDA meeting to discuss NDA. Proposed October 5, 1987. Postal receipt dated ?

8/17/87 Telephone Call Report:(MK/FDA). 90-day post-NDA meeting is scheduled for 10/15/87.

8/19/87 Letter:FDA/MK. Acknowledges receipt of ioversol NDA. Received 6/26/87.

#	DATE	DESCRIPTION
	9/9/87	Statistical and Cross Referencing (MI/FDA) Includes two volumes (1) Frequency Distributions of Extreme Changes in Vital Signs, ECG, and BP Data Associated with Injection of Contrat Media and (2) Phase II Clinical Data Summary (Vol. 15, pages 26-217) with additional cross referencing.
	9/11/87	Letter (FDA/MI) Bropharm review on Ioversol NDA 19-710. MI's response (amendment) is needed for items 1-6 under IV, last page (in triplicate)
	9/16/87	Letter (MI/FDA) Confirm 90-day conference to discuss the progress and review status. Meeting is scheduled for 10 am 10/15/87 and gives MI representatives. Postal receipt received 9/21/87.
	9/24/87	Memo (MI/MI) FDA compliance review of the ioversol facility plans.
	10/15/87	FDA minutes of 90-day conference.

Roll #	Date	Description
	10/16/87	Letter: MK/FDA. Confirming telephone conversation with Bob West, asked to arrange a meeting to discuss the chemistry review. Propose second week in December and giving MI attendees. PR dated 10/20/87.
	10/16/87	Four-Month Safety Update Report: MI/FDA. 149 patients in study after filing of NDA, 99 received ioversol. No safety information affecting the package insert is reported. Five studies, since filing of NDA, are now complete; 2 studies were added. PR 10/20/87
	10/21/87	Letter: MI/FDA. Enclosing additional copies of Volumes 2.15 and 2.20 - 2.31.
	10/26/87	Letter: MI/FDA. Sent case report forms for Study 207.
	11/4/87	Telephone Call Report:FDA/MI. Bob West confirmed our chemistry 90-Day meeting for 12/10/87, 1:30 pm, Conference Room H.
	11/5/87	Telephone Call Report:FDA/MI. Dr. Turner, Div. of Scientific Investigation requested a copy of case report forms and two copies of protocols for studies by Dr. Hirshfeld and Dr. Bettmann to be used in their audits.
	11/6/87	Statistical Data: MI/FDA. Sent directly to Dr. Hoberman. Changes in hemodynamic parameters. PR dated 11/12/87.
	11/9/87	Case Report Forms:MI/FDA. Sent case report forms and protocols for study 232 (Dr. Hirshfeld) and 207 (Dr. Bettmann) to Dr. Turner, Div. of Scientific Investigation.
	11/30/87	Letter (MI/FDA) Notification that C. Ray Holman will also attend Dec. 10 Mtg. to discuss progress of the chemistry review.
	11/25/87	MI sent FDA minutes of the 90-day ioversol Mtg. held at FDA on 10/15/87. A chemistry meeting will be held on 12/10/87.
	12/7/87	Amendment to NDA providing two genetic toxicity studies of MP-104 in vitro mouse lymphoma assay, and in vitro chromosomal obernation assay. PR received 12/15/87.
	12/16/87	Telephone contact. Marty James and Dr. Hoberman re statistical treatment of data.
	12/23/87	Letter (MI/FDA) Sending MI's version of minutes of 12/10 Mtg. discussing current status of the chemistry review. PR dated 12/28/87. Postal receipt received 12/28/87.

ROLL #	DATE	DESCRIPTION
	1/11/88	Telephone Call Report (MI/FDA) Jeff Dunn and FDA chemist Dr. Hubert Keily; discussed some aspect of 12/10/87 meeting, most particularly plane of symmetry and stereoisomers.
	1/28/88	Meeting Minutes (FDA/MI) Received FDA minutes of 12/10/87 chemistry review meeting.
	2/1/88	Telephone Conversation (MI/FDA) IND Amendments should be serial numbered starting with "001" even for INDs active prior to the IND rewrite regulations. Amendments already submitted without serial numbers, even with the new FDA 1571, should not be retroactively numbered.
	2/2/88	Telephone Call Report (FDA/MI) Re USP particulate matter test requirements.
	2/3/88	Statistical Information (MK/FDA) letter from Marty James to Dr. Ju. Postal receipt received 2/8/88.
	2/9/88	Statistical Information (MK/FDA) Information sent directly to Dr. Ju at his request to Marty James. Acknowledgement receipt 2/11/88.
	2/17/88	Statistical Data (MK/FDA) Information from Marty James to Dr. Ju and Dr. Hoberman. Acknowledgement letter 2/18/88.
	2/26/88	Statistical Data (MI/FDA) Information sent from Marty James to Dr. Ju. Acknowledgement letter received 2-29-88.
	1/13/88	Telephone Call Report (FDA/MI) Dr. Hoberman asked for confidence limits for the differences between ioversol and reference drug.
	2/29/88	Telephone Call Report (FDA/MI) Dr. Hoberman requested plots showing average change from baseline over time for hemodynamic parameters following coronary injection, and plots showing differences between drug groups with respect to those changes over time.
	3/8/88	Telephone Call Report (MI/FDA) Bob West reported chemistry review has been completed, reviewed by Dr. Wood and being typed. He agreed to forward copy of draft report in about one week.
	3/10/88	Telephone Call Report (FDA/MI) Dr. Ju requested photocopies of case report forms for patients in cerebral studies 206 and 213 who had changes in neurological status post-procedure relative to preprocedure baseline.
	3/14/88	Letter (MI/FDA) Dr. Ju forwarding, at his request, specific case report forms on cerebral studies 206 and 213. The CRFs requested represent patients that the investigator noted had changes in neurological status post-procedure relative to the pre-procedure baseline. Postal receipt received 3/17/88.

Roll #	Date	Description
	3/16/88	Telephone Call Report (MI/FDA) Bob West stated chemistry review is typed but not proofed. An unofficial copy of the unproofed review will be forwarded.
	3/21/88	Draft Chemist's Letter (FDA/MI) Received from FDA detailing five questions for drug substance, 12 questions for drug product, two for package insert.
	3/25/88	Statistical Data (MI/FDA) Submitted to Dr. Hoberman with a copy to Dr. Ju. Acknowledgement letter received 3/23/88.
	4/15/88	Telephone Call Report (FDA/MI) Telephone call with Dr. Ju of FDA. Discussed (1) when a comparative agent is used which is not marketed in the U.S., the ioversol data is merely suggestive; (2) studies which were ongoing or incomplete when NDA was submitted will have the remainder of data submitted after FDA approval; (3) Mallinckrodt is prepared to type FDA material on Wang equipment, as we had done before.
	4/15/88	Letter (MI/FDA) Amends Ioversol NDA. This amendment answers FDA's chemist's draft letter for drug product, part of which is also referenced in Raleigh DMF 2316. Drug substance answers are in DMF 6972. Acknowledgement letter dated 4/18/88.
	4/21/88	Telephone Call Report(FDA/MI) Call from Bob West, FDA. He wants MI to specifically state in writing which medical indications we want for early NDA approval, and which are considered supplements.
	4/21/88	Letter (FDA/MI) Gives deficiencies on chemistry, labeling, and biopharmaceutics. This is the "official" letter representing the same deficiencies received earlier for chemistry (3/21/88) and biopharmaceutics (9/17/88).
	4/26/88	Letter (MI/FDA) references telephone call report of 4/21/88. MI agrees that remaining indications submitted in the original NDA will be submitted as a supplement following NDA approval. P.R.dated 5/5/88.
	5/3/88	Telephone Call Report (MI/FDA) Called Bob West stating that biopharmaceutics answers were delayed. West said all should be sent in together.
	5/3/88	Telephone Call Report (MI/FDA) Called Dr. Keily to determine how he was progressing on review of our answers to the chemistry questions.
	5/6/88	Telephone Call Report (MI/FDA) Called Dri Keily to check status of chemistry review.

Roll #	Date	Description
	5/9/88	Letter (FDA/MI) Letter from FDA informing MI that the 4/15/88 amendment to NDA will require 60 days for review. The due date is now 6/17/88.
	5/13/88	Telephone Call Report (MI/FDA) Contacted Dr. Keily to inquire status of review of chemistry portion. Hopes to turn his comments in to Dr. Wood by Monday.
	5/13/88	Telephone Call Report (MI/FDA) Dr. Ju gave a progress report on his review of the additional clinical indications.
	5/16/88	Amendment (MI/FDA) Answers to Biopharmaceutics questions from FDA letter of 4/21/88. P.R. dated 6/1/88 Stamped acknowledgment letter dated 5/17/88.
	5/18/88	Telephone Call Report (MI/FDA) Telephone call with Bob West. Rebecca Wood is trying to clear up some chemistry issues with the reviewer before issuing the questions to us.
	5/20/88	Telephone Call Report (MI/FDA) Telephone call to Bob West discusses that the 4/15/88 amendment to the NDA will be forwarded to the microbiologist for review.
	5/20/88	Draft of Chemist's Letter lists 8 drug substance questions and 10 drug product questions (including one methods validation question).
	6/6/88	Telephone Call Report (FDA/MI) Dr. Ju called to discuss the format of the ioversol package insert and the clinical summary.
	6/10/88	Desk Copy Biopharmaceutics (MI/FDA) Sent a copy of Biopharmaceutics section of original NDA to Dr. Randy Dawkins. Vol. 14 of original NDA.
	6/3/88	Telephone Call Report (MI/FDA) Discussion of chemistry questions with Dr. Hubert Keily.
	6/10/88	Telephone Call Report (FDA/MI) Bob West asked for copy of Biopharmaceutics Section of original NDA be sent to Dr. Dawkins and for status of answer to chemistry questions.
	6/10/88	Telephone Call Report (FDA/MI) Dr. Ju requested certain summary tables (demography, dose and adverse reactions) that are based on studies which were complete at the time of the NDA submission for each indication, and for all indications combined.

ROLL #	DATE	DESCRIPTION
	6/16/88	Telephone Call Report (FDA/MI) from Bob West asking MI to prepare the SBA on Wang diskette. He also discussed that the package insert review is almost complete and he wants proposed advertising when the review is complete; he is sending out the official chemist's typed letter to match the handwritten letter we recently received; the biopharmaceutics review will be complete tomorrow; the microbiologist will start her review as soon as possible.
	6/20/88	Letter (FDA/MI) typed version of FDAs chemist letter - same questions as on 5/20/88
	6/21/88	Telephone Call Report (MI/FDA) call to Bob West, FDA, clarifying that Mallinckrodt will write the SBA.
	6/22/88	Revised Adverse Reaction Tables (MI/FDA) Sent to Dr. Ju by Marty James. Tables revised to exclude data from studies not complete at time of NDA submission.
	6/30/88	Letter (FDA/MI) Official deficiency letter based on review of 4/15/88 amendment. (Handwritten draft received 5/20/88, typed draft received 6/20/88, wording the same).
	7/1/88	Telephone Call Report (FDA/MI) from Dr. Ju requesting data relative to: 1) administration of heparin in coronary patients 2) changes in BUN and creatinine at 72 hours post injection of contrast
	7/7/88	Telephone Call Report (MI/FDA) with Dr. Ju who stated that he wants the SBA to exclude incomplete studies.
	7/15/88	Amendment (MI/FDA) provides answers to chemist's questions of 6/30/88
	7/18/88	Letter (MI/FDA) Letter to Dr. Ju regarding heparin administration and BUN and creatinine determinations.
	7/22/88	Telephone Call Report (MI/FDA) informing FDA Bob West of Mallinckrodt sending answers to chemist's questions of 6/20/88
	7/26/88	Telephone Call Report (MI/FDA) confirmed that all eight indications submitted in the original NDA have been reviewed by FDA
	8/9/88	Telephone Call Report (MI/FDA) to Dr. Eric Sheinin to discuss reviewing chemist for NDA.
	8/9/88	Telephone Call Report (MI/FDA) with Bob West. Chemistry answers have not yet been assigned a reviewer. Dr. Keily is not available for the review. Vivian Greenman has not started the microbiology review.

ROLL #	DATE	DESCRIPTION
	8/15/88	Letter (MI/FDA) Safety Update report requested by FDA. No new safety information that affects package insert - No deaths. Postal receipt dated 8/18/88.
	8/17/88	Telephone Call Report (FDA/MI) Discussed that FDA has not yet identified a chemist for the chemistry review of MI's 7/20/88 response. Dr. Palmer is considering writing a memo to Kumkumian discussing that Vivian Greenman has not yet started the microbiology review.
	8/23/88	Telephone Call Report to Bob West: Drs. Temple and Palmer will try to expedite the micro review by talking to the Division head of Surgical-Dental; they will similarly try to get Keily to finish the chemistry review.
	8/24/88	Telephone Call Report (MI/FDA) 1. Review of chemistry and microbiology status with Dr. Jerussi. 2. Review of ANDA status with Dr. Jerussi.
	8/31/88	Telephone Call Report (MI/FDA) Asking Dr. Jones current status of MOR. MOR is on his desk. Gave no indication as to when review will be made.
	9/1/88	Telephone Call Report with Bob West discusses that Vivian Greenman started the micro review on 8/31/88. Dr. Palmer discussed chemistry with the Surgical-Dental Director, and Kiely "may" be the reviewer.
	9/7/88	Telephone Call Report with microbiologist Vivian Greenman who questioned the 4/15/88 submission (p. 57, 73) where MI used 50 mL vials as worst case for validation.
	9/7/88	Telephone Call Report from Bob West, who asked Niles Ross to call Vivian Greenman, microbiologist. FDA has not yet identified a chemist to continue the review of the NDA.
	9/16/88	Letter from FDA asking for additional information for safety update.
	9/19/88	Telephone Call Report (FDA/MI) Vivian Greenman's draft micro review is complete. MI will pick up.
	9/19/88	Draft of Vivian Greenman's microbiology questions Four questions deal with process parameters, heat distribution, min/max Fo, heat resistance of spore lot used in validation.
	9/20/88	Telephone Call Report (FDA/MI) Dr. Keily has not started chemistry review. FDA's 9/16/88 request for advertising should be ignored. FDA has not finalized the MOR.
	~~9/21/88~~	~~Protocols (MI/FDA) Two protocols for pediatric patients sent to Dr. Ju.~~

moved to Ioversol IND 27,630

Roll #	Date	Description
	10/13/88	Telephone Call Report (MI/FDA) With Bob West. Dr. Jones is on vacation this week, but has taken the MOR with him to review. Dr. Keily will start his review by the end of the month.
	10/19/88	Telephone Call Report (FDA/MI) From Bob West. We discussed that the safety update went out today, and the answers to the microbiology questions will go out next week. He said the MOR is not yet signed, but we should draft the SBA in advance and edit it for changes when the MOR is issued. We discussed that MI would send the SBA on Wang diskettes.
	10/19/88	Amendment to NDA (MI/FDA) Provides safety update report in response to FDA's 9/16/88 letter. Provides data on the 6 clinical studies (244 patients) which were completed after NDA filing. PR received dated 10/24/88.
	10/21/88	Telephone Call Report (MI/FDA) With Bob West who wants us to send our SBA to him AFTER the MOR is final, so we will be able to format the SBA like the MOR.
	10/28/88	Telephone Call Report (MI/FDA) Called Dr. Keily on status of chemistry review. Review should be completed in 2 weeks.
	10/31/88	Letter (MI/FDA) Answers the 9/18/88 draft microbiology questions: heat history profiles; performance specifications for time/temperature parameters; F_o range; D and Z values.
	11/1/88	Telephone Call Report (MI/FDA) To Bob West states that MOR is not yet released. SBA will have to follow MOR format.
	11/2/88	Telephone Call Report (FDA/MI) Call from Bob West requesting Mallinckrodt forward to Vivian Greenman the section of the NDA dealing with pyrogenicity.
	11/2/88	Submission (MI/FDA) Sent to Vivian Greenman that portion of NDA that deals with Pyrogen testing. PR received dated 11/6/88.
	11/3/88	Telephone Call Report (MI/FDA) Called Bob West. Discusses that we should receive one section of the MOR next week.
	11/3/88	Amendment (MI/FDA) to 10/31/88 microbiology answers - provides new package to correct clerical errors.
	11/3/88	Telephone Call Report (MI/FDA) Requested draft copy of MOR in order to see format for SBA.
	11/10/88	Amendment (MI/FDA) Submitted In Vitro clotting report to NDA.
	11/16/88	Telephone Call Report (FDA/MI) Vivian Greenman had detailed questions concerning raw data regarding our 10/31/88 submission. She asked to speak with Steve Holden.
	11/18/88	Draft MOR (FDA/MI) For IA-DSA indication studies 240 (Miller) and 246 (Heggelman).

Date	Description
11/17/88	Telephone call with Vivian Greenman (FDA) and Steve Holden clarifying the 10/30/88 micro submission.
11/22/88	Answers to Questions (MI/FDA) Refers to Dr. Greenman's questions. Formal submission of answers faxed and sent to Dr. Greenman 11/16/88 by Steve Holden.
11/23/88	Telephone call with Vivian Greenman (FDA) and Steve Holden - Vivian Greenman finished her review of microbiology.
11/30/88	Telephone Call Report (FDA/MI) Bob West informs MI that a meeting is scheduled 12/2/88, 1 p.m. on the PI. Also informs MI that Dr. Keily's review is complete.
11/30/88	Telephone Call Report (MI/FDA) Bob West reported V. Greenman has completed her review and Dr. Keily has completed the chemistry review. A meeting will be held on Package Insert today. More details will follow.
12/1/88	Telephone Call Report (MI/FDA) Bob West called giving Dr. Keily's chemistry questions. MI is informed that questions will be reviewed by Eric Sheinin.
12/1/88	Telephone Call Report (FDA/MI) Bob West called clarifying Question #2 of chemist's notes.
12/2/88	Addendum (FDA/MI) FDA provided an explanatory addendum to Dr. Keily's chemistry question 6.
12/8/88	Letter (MI/FDA) Draft advertising to Division of Drug Advertising.
12/8/88	Letter (MI/FDA) Package insert, advertising, summary basis of approval - drafts to Division of Oncology and R/P.
12/12/88	Response to draft chemistry questions received 12/1/88. (MI/FDA) Response includes a compilation of all validation reports submitted to date.
12/14/88	Telephone Call Report (MI/FDA) Notified Dr. Jerussi that our response to FDA's last round of questions delivered 12/13. Dr. Jerussi stated FDA trying to wrap up approval of NDA by the end of the year.
12/14/88	Telephone Call Report (FDA/MI) MI requested to remove Optiray-240 indications for IA-DSA and head and body CT. No controlled studies. FDA can only accept clinical studies. If we can gather data - submit as a supplement.
12/15/88	Telephone Call Report (MI/FDA) Spoke with Bob West. FDA, Squibb, Winthrop, have not reached agreement on clotting. MI can go on the market with the current insert. A task force will be formed to look into the clotting issue. The last proposed FDA statement is in the report.
12/19/88	Draft Package Insert (MI/FDA) Revised according to discussion with Dr. Ju and Bob West.
12/21/88	Amendment (MI/FDA) Provides reports on viscosity, osmolality and specific gravity.

Date	Description
12/30/88	Letter (FDA/MI) Approval letter effective 12/30/88.
1/3/89	Telephone Call Report (MI/FDA) B. West stated ioversol approval letter signed 12/30/88. The letter asks for 3 package insert corrections. Dr. Botstein has not finished the SBA.
1/11/89	Telephone Call Report (MI/FDA) Bob West requests a single bottle and a single vial of each strength, each with a package insert, when available.

877-708
GRR:585

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of)
Youlin Lin)
U.S. Patent 4,396,598)
Issued: August 2, 1983)
For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT)

DECLARATION OF NILES B. ROSS

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Niles B. Ross, declare that:

1. I am Senior Regulatory Affairs Associate with Mallinckrodt, Inc., assignee of the above-identified U.S. Patent.

2. I have overseen obtaining FDA approval for the x-ray contrast agent claimed in the above-identified U.S. Patent.

3. To the best of my knowledge, information and belief, the chronologies of activities concerning IND 27,630 and NDA 19-710, respectively set forth in Exhibits G and H of the accompanying Application for Extension of Patent Term under 35 USC 156, are accurate and correct.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made are information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent.

2/3/89
Date

Niles B. Ross

ATTACHMENT J

CALCULATION OF LENGTH OF PATENT TERM EXTENSION FOR A HUMAN DRUG PRODUCT

1.	ENTER THE NUMBER OF DAYS FOR THE TESTING PHASE AS DEFINED IN 37 CFR 1.775(c) (1)	519	
2.	ENTER THE NUMBER OF DAYS FOR THE APPROVAL PHASE AS DEFINED IN 37 CFR 1.775(c) (2)	554	
3.	ADD LINE 1 AND LINE 2 AND ENTER THE TOTAL HERE		1073
4.	ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
5.	ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 2 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d) (1) (ii)	0	
6.	ADD LINE 4 AND LINE 5 AND ENTER THE TOTAL HERE		0
7.	SUBTRACT LINE 6 FROM LINE 3 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")		1073
8.	ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 WHICH OCCURRED PRIOR TO THE ISSUE DATE OF THE PATENT	0	
9.	ENTER THE NUMBER OF DAYS OF THE PERIOD OF LINE 1 DURING WHICH THE APPLICANT FAILED TO ACT WITH DUE DILIGENCE AS DEFINED IN 37 CFR 1.775(d) (1) (ii)	0	
10.	ADD LINE 8 AND LINE 9 AND ENTER THE TOTAL HERE		0
11.	SUBTRACT LINE 10 FROM LINE 7 AND ENTER THE DIFFERENCE HERE		1073
12.	ENTER THE NUMBER OF DAYS FROM LINE 1	519	
13.	ENTER THE NUMBER OF DAYS FROM LINE 10	0	
14.	SUBTRACT LINE 13 FROM LINE 12 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")	519	
15.	MULTIPLY LINE 14 BY 0.5 (ONE HALF) AND ENTER THE AMOUNT HERE		260
16.	SUBTRACT LINE 15 FROM LINE 11 AND ENTER THE DIFFERENCE HERE (IF LESS THAN ZERO ENTER "0")		813
17.	ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT	8-2-2000	
18.	ENTER THE EXPIRATION DATE OF PATENT IF EXTENDED BY THE NUMBER OF DAYS ON LINE 16	10-24-02	
19.	ENTER THE DATE OF THE FDA (FOOD AND DRUG ADMINISTRATION) FINAL APPROVAL	12-30-88	
20.	LIMITATION SET FORTH IN 37 CFR 1.775(d) (3)	14 YEARS	
21.	ADD THE NUMBER OF YEARS ON LINE 20 TO THE DATE ON LINE 19 AND ENTER THE REVISED DATE HERE	12-30-02	
22.	ENTER THE EARLIER DATE APPEARING ON LINE 18 OR LINE 21		10-24-02
23.	ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)	8-2-2000	
24.	CHECK ONE OF THE FOLLOWING THREE BOXES AND ENTER THE LISTED TIME PERIOD HERE	5	
	☐ THE PATENT ISSUED AFTER 09/24/84	5 YEARS	
	☐ THE PATENT ISSUED PRIOR TO 09/24/84 AND NO REQUEST FOR EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (i) WAS FILED PRIOR TO 09/24/84	5 YEARS	
	☐ THE PATENT ISSUED PRIOR TO 09/24/84 AND AN EXEMPTION AS DEFINED IN 37 CFR 1.775(d) (6) (ii) WAS FILED PRIOR TO 09/24/84	2 YEARS	
25.	ADD THE NUMBER OF YEARS ON LINE 24 TO THE DATE ON LINE 23 AND ENTER THE REVISED DATE HERE	8-2-05	
26.	ENTER THE EARLIER DATE APPEARING ON LINE 22 OR LINE 25		10-24-02
27.	ENTER THE ORIGINAL EXPIRATION DATE OF THE PATENT (FROM LINE 17)		8-2-2000
28.	ENTER THE NUMBER OF DAYS BY WHICH LINE 26 AND LINE 27 DIFFER HERE THIS IS THE LENGTH OF PATENT TERM EXTENSION		813

EXHIBIT J
4,396,598

877-708
TT/051

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,396,598

Issued: August 2, 1983

To: Youlin Lin

For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT

DECLARATION PURSUANT TO 37 CFR §1.740(a)(17)

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

The undersigned attorney for Mallinckrodt, Inc., the Applicant for Extension of Patent Term under 35 U.S.C. §156 with regard to U.S. Patent 4,396,598 hereby declares as follows:

(1) THAT he is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in patent matters;

(2) THAT he has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.740;

(3) THAT he believes the patent is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710;

(4) THAT he believes that an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

(5) THAT he believes the patent for which the extension is being sought (U.S. Patent 4,396,598) meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. §156 and 37 C.F.R. §1.720.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that

willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2/2/89

Roy J. Klosterman
Registration No. 25,349

Mallinckrodt, Inc.
675 McDonnell Blvd.
St. Louis, MO 63134
(314) 895-2915

877-708
GRR:585

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of	)
Youlin Lin	)
U.S. Patent 4,396,598	)
Issued: August 2, 1983	)
For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT	)

ASSOCIATE POWER OF ATTORNEY

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

The undersigned attorney of record in the above-identified patent, on behalf of Mallinckrodt, Inc., assignee of the above-identified patent, hereby appoints the following attorneys as associate attorneys to prosecute and transact all business in the Patent and Trademark Office connected therewith:

Eugene L. Bernard, Reg. No. 18,960
G. Franklin Rothwell, Reg. No. 18,125
E. Anthony Figg, Reg. No. 27,195
Donald W. Marks, Reg. No. 24,218
Frank L. Neuhauser, Reg. No. 14,975
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Bart G. Newland, Reg. No. 31,282
William T. Enos, Reg. No. 33,128

Please send all correspondence about the patent to Eugene L. Bernard, BERNARD, ROTHWELL & BROWN, P.C., 1700 K Street, N.W., Washington, D.C 20006, Telephone No 202/833-5740.

All other previously granted powers of attorney remain in effect. I am authorized by Mallinckrodt, Inc. to execute this document.

Respectfully submitted,
Mallinckrodt, Inc.

Roy J. Klostermann
Reg. No. 25,349

675 McDonnell Blvd.
St. Louis, Missouri 63134
Tel. No. (314) 895-2915

877-708
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,396,598

Issued: August 2, 1983

To: Youlin Lin

For: TRIIODOISOPHTHALAMIDE X-RAY CONTRAST AGENT

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. §156 including its attachments and supporting papers is being submitted as one original and a duplicate copy thereof.

George R. Repper
Attorney for Applicant
Registration No. 31,414

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Dated: 2-8-89